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Titre :

ELLE & IL:

Enantioselective Liquid-Liquid Extraction and Ionic Liquids

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Abstract

Enantioselective liquid-liquid extraction (ELLE) is an implementation of the extraction of one enantiomer from a racemic mixture by the transfer between two liquid phases. This technology is very promising for obtaining enantiopure compounds and becomes the object of much attention in recent years after the development of appropriate equipment that reduces the time and cost of the separation of enantiomers. The major objective for the successful introduction of ELLE to industrial world is the discovery of reliable, inexpensive and durable chiral hosts selective for a wide range of chiral substances. In this work the possibility of performing ELLE in chiral ionic liquids environment was verified. Many new chiral ionic liquids were prepared to play the role of chiral hosts. The best example shows enantiomeric excess of 30% and operational selectivity of 1.97. This represents the first example of using chiral ionic liquids in ELLE and without metallic ions.

Keywords: Ionic liquids; Chirality; Enantioselectivity; Liquid-Liquid Extractions.

Résumé

L'extraction liquide-liquide énantiosélective (ELLE) consiste en l'extraction d'un énantiomère à partir d'un mélange racémique par transfert entre deux phases liquides. Cette technologie est très prometteuse pour l'obtention des composés énantiopurs et devient l'objet d'une forte attention les dernières années grâce au développement de l'équipement approprié qui permet de réduire le temps et le prix de la séparation des énantiomères. L'objectif essentiel pour l'introduction d'ELLE dans le monde industriel est la découverte d'hôtes chiraux fiables, peu chers, durables, sélectifs et applicables à une large gamme de substances chirales. Dans ce travail, la possibilité d'effectuer l'ELLE dans un milieu ionique chiral a été vérifiée. De nombreux nouveaux liquides ioniques chiraux ont été préparés pour jouer le rôle des hôtes chiraux. Le meilleur exemple montre un excès énantiomérique de 30% et une sélectivité opérationnelle de 1,97. Ceci représente le premier exemple d'ELLE utilisant les liquides ioniques chiraux et sans usage d'ions métalliques.

Mots-clés: Liquides ioniques; Chiralité; Énantiosélectivité; Extractions Liquide-Liquide.

1 Contents

2 Introduction

Le but de cette recherche a été de vérifier la possibilité de l'extraction liquide-liquide énantiosélective par les liquides ioniques chiraux.

Cette introduction explique brièvement l'idée, son importance, son support et la logique des actions. Dans la partie bibliographique, les arguments qui nous ont dirigés vers l'idée de l'extraction liquide-liquide énantiosélective par les liquides ioniques chiraux sont décrits. La partie de discussion raconte le progrès de ce projet étape par étape ainsi que les résultats obtenus. La conclusion résume les résultats obtenus. La partie expérimentale précise les méthodes et les appareils utilisés et donne les caractéristiques des composés obtenus. Dans l'information supplémentaire les articles écrits pendant la période de cette recherche sont ajoutés.

La chiralité est la propriété de certains objets d'exister sous deux formes isomères qui correspondent à deux images dans un miroir, et qui ne sont pas superposables. Par exemple, une main est un objet chiral avec deux énantiomères : la main droite et la main gauche. La distribution d'atomes différents dans l'espace, par exemple autour d'un point, peut conduire à des images non superposables dans un miroir, donc des objets différents (Figure 2-1).

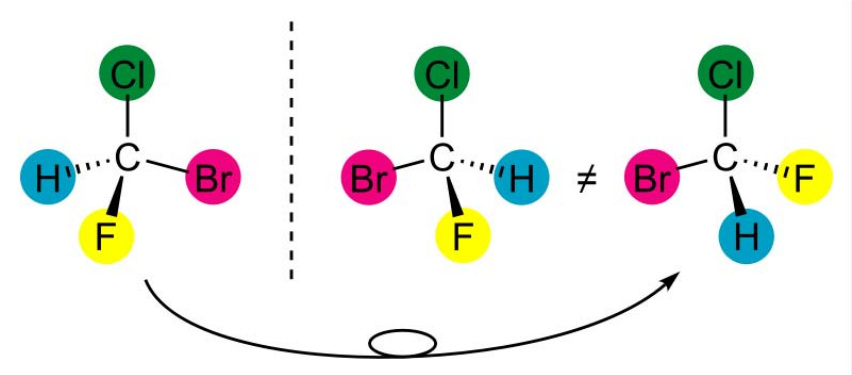


Figure 2-1. Exemple d'une molécule chirale. Les deux premières molécules sont l'image dans un miroir l'une de l'autre. Si on tourne la première on voit qu'elle n'est pas superposable à la seconde.

Les deux énantiomères sont extrêmement difficiles à séparer car ils possèdent les mêmes propriétés physiques: solubilité, température d'ébullition, etc. Ils peuvent cependant être différenciés par une propriété optique, la déviation de la lumière polarisée: l'un des composés

la dévie à droite, et l'autre la dévie à gauche et avec la même valeur absolue. Louis Pasteur a montré en 1848 que l'activité optique est liée à la chiralité[1].

La disponibilité des composés énantiopurs est indispensable pour l'industrie pharmaceutique et dans une certaine mesure pour l'agrochimie, l'industrie alimentaire et la parfumerie. Les énantiomères peuvent être obtenus soit par une approche synthétique soit par la séparation de racémiques. En dépit du faible prix des synthèses basées sur les «pools chirals» et la grande performance de la catalyse asymétrique, la séparation de racémiques domine dans l'industrie sur les approches synthétiques[2].

Il peut être très surprenant pour un chimiste organicien de constater que l'application de méthodes asymétriques est assez restreinte dans le monde industriel. Par exemple, la catalyse asymétrique dans l'industrie est limitée à une douzaine de cas. En tout en 2001, il y avait seulement 16 processus industriels et 37 pilotes utilisant la catalyse asymétrique[3]. Cela est dû au fait que le temps d'arrivée sur le marché pour la séparation de racémiques est potentiellement plus court que la catalyse asymétrique. La séparation des racémiques peut être faite avec une technique qui est largement applicable à une grande diversité des substrats.

La façon avec laquelle deux chimistes organiciens, du laboratoire et de l'industrie, s'approchent du problème de synthèse est très diffèrente. Quand au laboratoire on cherche plutôt la «beauté» de la voie synthétique (qui comprend un petit nombre d'étapes et des rendements élevés), dans l'industrie on va chercher à réduire le prix et à minimiser le temps du procédé (Figure 2-2). Une synthèse facile des composés racémiques suivie par une séparation de racémique en utilisant une technologie largement applicable peut être facilement développée, donc devenir éventuellement très bénéfique.

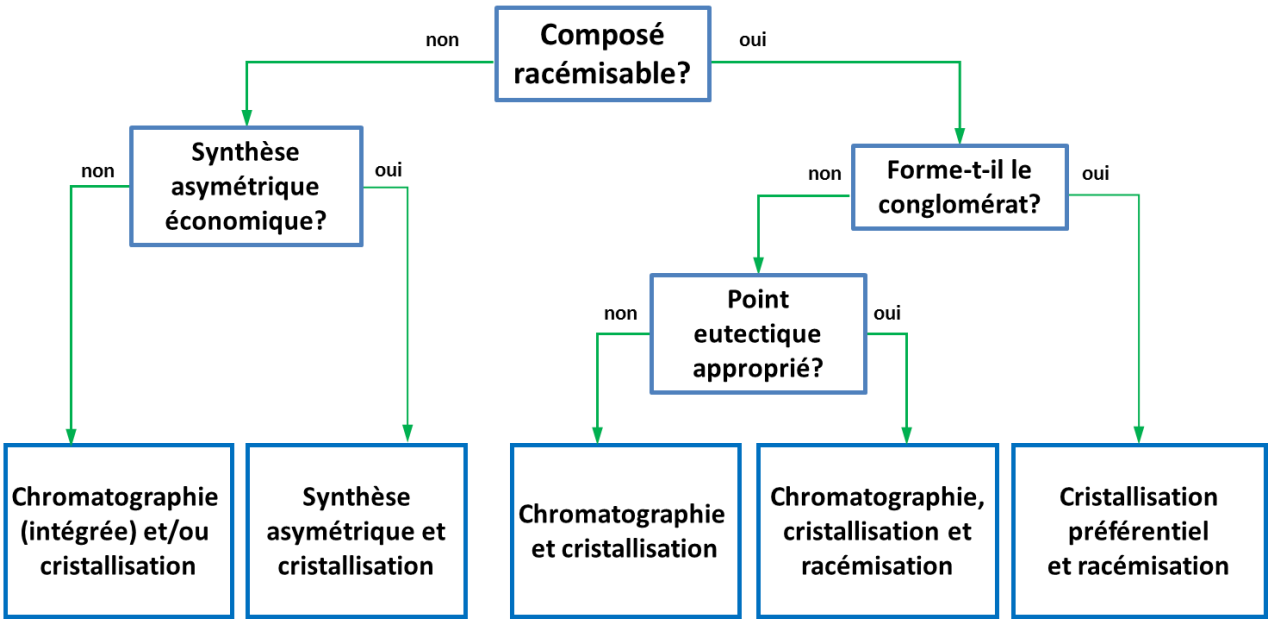


Figure 2-2. Arbre de décision pour le choix qualitatif de procédé dans l'industrie[4]. Avec la permission de M. Hedberg (AstraZeneca).

Dans l'arbre de décision utilisé dans l'industrie pour le choix qualitatif de procédé (Figure 2-2), la première question posée par un chimiste industriel concerne la possibilité pour le composé d'être racémisé. Quand la racémisation est possible l'approche de la synthèse asymétrique sera rejetée pour libérer la voie aux méthodes généralement utilisées pour séparer les racémiques.

Les méthodes traditionnelles de la séparation de racémiques comprennent la cristallisation de sels diastéréoisomères, la chromatographie chirale et le dédoublement enzymatique. La séparation des mélanges racémiques à l'échelle industrielle est généralement basée sur un dédoublement par cristallisation. Chacune de ces méthodes peut avoir certains avantages (efficacité, fonctionnalité, économie, etc.) sur les autres pour un composé chiral particulier. Toutefois, la sélection et l'optimisation de la méthode peut prendre du temps et des efforts considérables pour chaque cas particulier et la procédure optimisée ne peut pas toujours être générale pour une certaine classe de composés chiraux.

Bien que le dédoublement par cristallisation soit la voie la plus fréquemment utilisée pour obtenir les composés énantiopurs, les principaux inconvénients sont la basse polyvalence, la gestion de quantités excessives de matières solides et le rendement maximal limité à 50% si la racémisation de l'énantiomère non désiré ne peut pas être appliquée[2]. Très pratique en laboratoire, la gestion de matières solides devient une difficulté pour les processus industriels qui traite les solides à l'échelle de tonnes. Souvent, c'est l'étape le plus lent de procède. Par

contre, l'utilisation de liquides en grande échelle ne pose aucun problème pour l'industrie chimique.

Par conséquent, il existe un besoin continu de chercher les stratégies alternatives générales pour le dédoublement des mélanges racémiques d'une manière peu chère, rapide et écologique. Une méthode prometteuse repose sur la capacité d'un sélecteur chiral de distinguer les deux énantiomères d'un racémique, ce qui rend la séparation énantiomérique de mélanges racémiques possible. Par exemple, par l'extraction liquide-liquide avec un hôte chiral.

Nous retrouvons l'idée de la reconnaissance chirale dans la mythologie grecque (Figure 2-3). La nymphe Echo (hôte chiral) veut se réunir avec Narcisse (énantiomère 1) qui, de son coté, veut partir dans la phase aqueuse pour se retrouver avec son image en miroir (énantiomère 2) pour former un racémique. Dans notre travail l'hôte chiral a été capable de séparer (au moins partiellement) un énantiomère de l'autre, à la différence du mythe original où l'hôte chiral se laissa dépérir en n'étant pas capable de séparer l'énantiomère 1 de son image en miroir.

Figure 2-3. ELLE & IL: Écho et Narcisse. John Waterhouse, Oil, 1903, Walker Art Gallery, Liverpool, UK. Cette métaphore est adaptée de Feringa et coll[5].

L'extraction liquide-liquide énantiosélective (ELLE) est une mise en œuvre de l'extraction d'un énantiomère à partir d'un mélange racémique par transfert entre deux phases liquides. ELLE combine les principes de la reconnaissance d'énantiomères et l'extraction dans une seule technique. Après l'opération, on récupère deux phases séparées par décantation : l'extrait

formé du solvant enrichi en soluté, et le raffinat, soit le mélange appauvri en soluté. L'utilisation de l'extraction liquide-liquide pour l'énantioséparation est connue depuis 1959 [6], mais le développement vers la commercialisation a été suspendu pendant plusieurs décennies jusqu'aux années 2000, principalement en raison de l'absence de l'équipement approprié[2].

L'avantage principal d'ELLE est qu'il n'y a pas besoin d'accomplir une séparation complète des énantiomères en une seule étape. Le processus de séparation satisfaisante peut être développé en utilisant la technologie basée sur le processus en plusieurs étapes de l'extraction à contre-courant. Grâce à cette technologie en plusieurs étapes, des composés énantiopurs peuvent être obtenus avec des rendements élevés en utilisant des sélecteurs qui possèdent des sélectivités modérées. Avec cette approche, il n'est pas nécessaire d'avoir une sélectivité importante en une seule étape, comme, par exemple dans la catalyse asymétrique.

Dans la littérature scientifique il y a plusieurs exemples réussis d'ELLEs. En 2011, il y avait 21 types d'hôtes chiraux différents utilisés pour les ELLEs, pour donner dans certains exemples des excès énantiomériques très élevées, combinés avec de très bons rendements en masse[2].

Les hôtes chiraux utilisés sont les éthers couronnes, les complexes de métaux, les tartrates, les diphosphoniums, les cyclodextrines, les alcaloïdes, les stéroïdes, etc. Aucun exemple d'utilisation des liquides ioniques chiraux n'était connu dans la littérature au début de ce travail. **Notre idée a été d'utiliser les liquides ioniques chiraux comme les hôtes de la reconnaissance chirale dans l'extraction liquide-liquide énantiosélective.**

Les liquides ioniques (LIs) sont des sels (habituellement organiques) possédant une température de fusion inférieure à 100 °C et souvent même inférieure à la température ambiante. Certains liquides ioniques sont à l'état liquide à température ambiante et sont appelés des liquides ioniques à température ambiante (Room-Temperature Ionic Liquid, RTIL), (Figure 2-4). Ces derniers ont des avantages pratiques vis-à-vis des liquides ioniques à haute température de fusion et sont donc plus utilisés.

Figure 2-4. Figure 4. Liquide ionique à température ambiante [bmim]NTf_2 et sel de table NaCl à 27°C.

Les LIs sont souvent considérés comme des solvants propres parce qu'ils possèdent une pression de vapeur nulle aux conditions ambiantes et sont donc non-volatils et permettent d'éviter les problèmes de sécurité et de pollution liés à l'évaporation du solvant. En plus, ils ne sont pas inflammables, ont de très bonnes capacités à la dissolution d'une vaste gamme de substances, y compris les biopolymères. Le nombre des LIs différents possibles à synthétiser virtuellement n'a pas de limite, et ces LIs peuvent être obtenus avec les propriétés prédéfinies d'avance. Les LIs peuvent être obtenus à partir de sources renouvelables, ne pas être toxiques et être non dangereux pour l'environnement et les humains. L'ensemble de toutes ses propriétés correspond aux douze principes de la chimie verte, ce qui rend l'utilisation des liquides ioniques très prometteuse[7].

Les liquides ioniques chiraux (LIC) sont des sels possédant une température de fusion inférieure à 100 °C et au minimum un élément de chiralité. L'utilisation de LIC peut être très avantageuse parce qu'ils peuvent être utilisés dans les ELLEs comme substituts aux solvants organiques traditionnels et comme les hôtes chiraux simultanément. Ce thème de recherche a été finance dans le cadre du projet européen INTENANT [8].

Synthèse intégrée et purification des énantiomères purs (INTegrated synthesis & purification of single ENANTiomers, INTENANT, Figure 2-5) est l'un des premiers projets de recherche financés dans le cadre de la septième session de programme de recherches (7th Framework Programme) de la Commission européenne[9]. Le projet a débuté le 1er juin 2008 et prend fin le 1er juin 2011. Il a entièrement financé ce travail de thèse.

Figure 2-5. Logotype d'INTENANT représentant les deux mains, objet chiral presentant deux énantiomères.

Un consortium de 13 groupes de travail sur 11 sites de l'Europe (Figure 2-6) a effectué des recherches scientifiques sur les substances énantiomériques. Les chercheurs de ce projet ont visé à simplifier la synthèse et la purification des substances énantiomères, qui sont nécessaires par exemple dans l'industrie pharmaceutique et alimentaire.

Figure 2-6. Les 11 partenaires du programme INTENANT.

Le contexte de la création du projet INTENANT a été lié à l'observation que deux concepts généraux coexistent pour la production d'un seul énantiomère. Le premier est le développement et l'application des techniques de la synthèse énantiosélective, le deuxième est la synthèse non-sélective en combinaison avec les techniques de séparation et les

stratégies de recyclage. Les deux concepts sont difficilement combinables et souvent pris en compte séparément. L'objectif du programme INTENANT consistait à créer une approche intégrée combinant les méthodes chimiques et physiques disponibles de façon efficace pour produire un seul énantiomère à haute pureté avec un bon rendement.

La stratégie d'INTENANT consistait en plusieurs approches:

- Former un consortium de groupes spécialisés dans les technologies individuelles (synthèse, séparation, racémisation).
- Ajouter l'expertise profonde en analyse mathématiques, la combinaison des processus et l'optimisation des procédés combinés.
- Etudier systématiquement des processus innovants, les options des procédés qui ne sont pas encore bien connus.
- Développer des systèmes facilement applicables pour le design de procédé.
- Sélectionner et étudier le modèle le plus prometteur et représentatif.
- Evaluer directement des concepts mis au point par les partenaires industriels.

Notre partie consistait en étude d'un processus innovant – l'extraction liquide-liquide énantiosélective. Dans la structure totale du projet nous avons participé dans deux modules de travail (Work Package, WP): WP2 et WP4 (Figure 2-7).

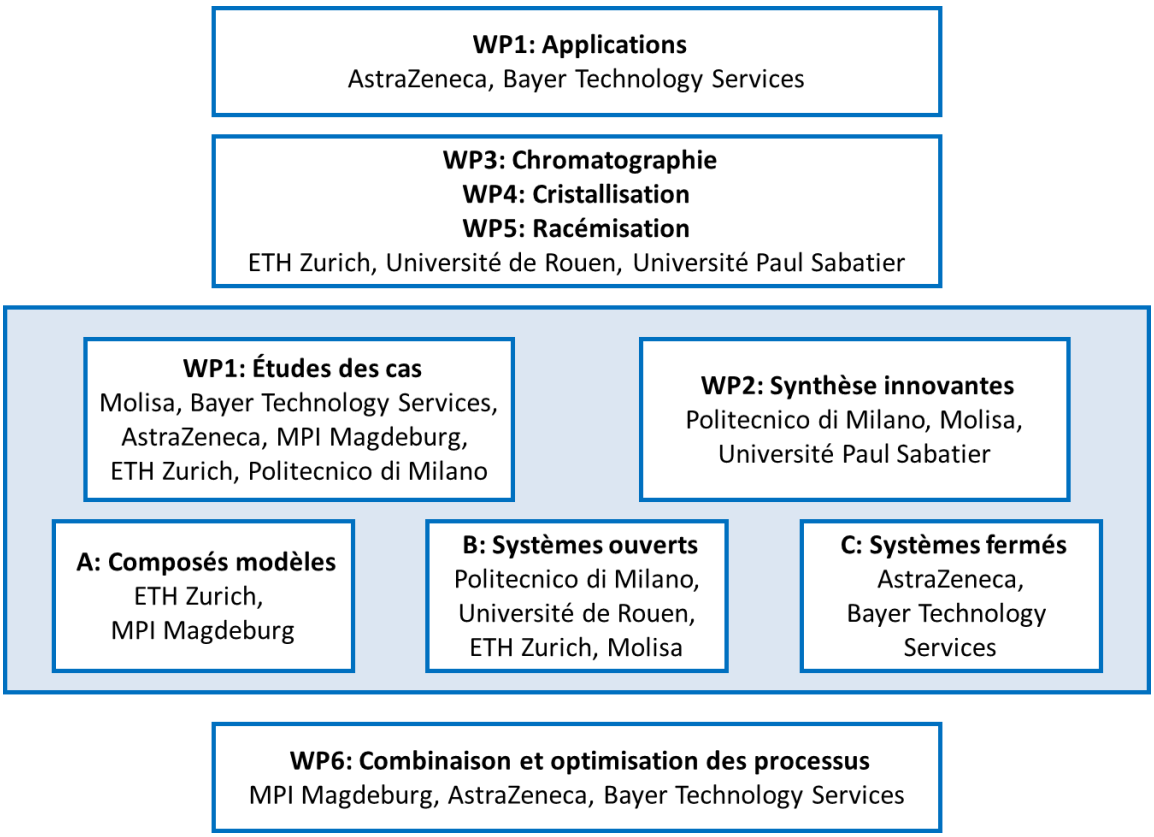


Figure 2-7. Structure du projet INTENANT.

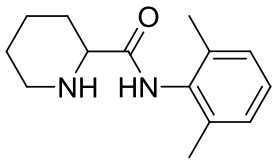
Chaque semestre, tous les groupes se réunissaient pour rapporter leurs résultats et coordonner les actions pour le futur. Les étudiants présentaient leurs progrès dans leur parcours de thèse, les scientifiques et les industriels exposaient leurs avancées.

Le plan de notre partie du projet consistait en:

1. Choix des substrats racémiques
2. Préparation d'hôtes chiraux - LIC
3. Choix des co-solvants LIs
4. Choix du deuxième solvant pour le système biphasique
5. Essais de solubilité des substrats choisis
6. Criblage de tous les substrats avec tous les hôtes
7. Etude des paramètres importants pour un système choisi

Chaque étape a été interconnectée avec les étapes précédentes. Par exemple le choix de liquides ioniques pour le rôle de co-solvants a été dépendant de la structure de liquides ioniques chiraux, et pour les choisir il était nécessaire de connaitre la structure de substrats racémiques...

Nous avons choisi de travailler avec un composé du groupe C (Systèmes fermés) nommé le pipecoloxylidide et possédant le code C3 (Figure 2-8). Il est un intermédiaire pour la synthèse d'une famille de médicaments commerciaux qui sont des anesthésiques locaux. En tout une vingtaine de substrats a été proposée par les partenaires industriels d'INTENANT.

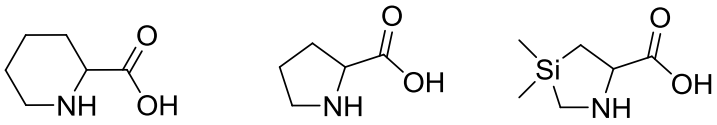


Pipecoloxylidide
Pipeco

Figure 2-8. Structure de pipécoloxylidide.

Le choix de la structure de ce composé a été fait parce qu'il contient la fonction amide, souvent présente dans un grand nombre de substances chimiques. Cette décision a été prise pour élargir le nombre de structures possibles dédoublables, et donc faciliter l'introduction d'ELLE dans les procédés industriels.

Avec le pipécoloxylidide trois autres structures ont été choisies comme substrats racémiques. L'acide pipécolique parce qu'il est le composé de départ dans la synthèse du pipecoloxylidide, son homologue naturel l'acide α-aminé proline et l'équivalent sylié de la proline – la silaproline[10] (Figure 2-9).



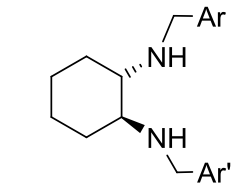
Acide pipecolique **Pip** | Proline **Pro** | Silaproline **Sip**

Figure 2-9. Les substrats racémiques à dédoubler.

Considérant qu'il n'y a que quelques exemples de liquides ioniques chiraux disponibles commercialement, une étape de notre recherche consistait en préparation de plusieurs liquides ioniques chiraux portant au moins une fonction capable d'interagir avec des substrats racémiques.

À cette fin, nous avons sélectionné le 1,2-diaminocyclohexane (DACH) comme synthon de départ. Dans la littérature, il y avait plusieurs exemples où il était utilisé pour la préparation d'agents de dédoublement énantiosélectif[11]. Donc on peut s'attendre à de fortes propriétés énantiodiscriminantes de liquides ioniques chiraux synthétisés en partant de DACH envers les

énantiomères de composés chiraux. Afin d'obtenir des liquides ioniques, les structures requises doivent posséder au moins une fraction pouvant être alkylée ou protonée. Nous avons donc choisi des dérivés de la pyridine DACH en tant que hôte chiral pour créer la nouvelle classe de liquides ioniques chiraux et les utiliser dans ELLEs (Figure 2-10).

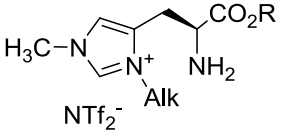


Ar = 2-pyridyl; 3-pyridyl;
4-pyridyl; phenyl
Ar' = 2-pyridyl; 3-pyridyl;
4-pyridyl

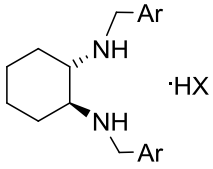
Figure 2-10. Les dérivés de 1,2-diaminocyclohexane (DACH).

Le deuxième but de la préparation de dérivés de DACH a été lié aux activités de recherche du module de travail WP4 d'INTENANT "La cristallisation". Les dérivés du 1,2-diaminocyclohexane synthétisés ont été planifiés pour servir dans les tests de cristallisation préférentielle effectués à l'Université de Rouen.

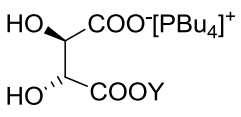
En tout, quatre familles des LIC ont été choisies pour notre projet, dérivés de: (*S,S*)-DACH; (*S*)-histidine; acide (*R,R*)-tartrique et (*R*)-phényléthylamine (Figure 2-11). Les trois premières familles ont été synthétisées par notre équipe, alors que le dérivé issu de la phényléthylamine a été commandé à la société Solvionic.



R= H; Me
Alk= Bu; Oct; Dodec



Ar = pyridyl; phenyl
X= NTf_2; PF_6; BF_4



Y= H; $[PBu_4]$

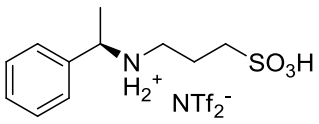
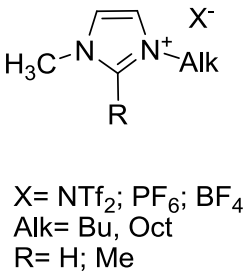


Figure 2-11. Les structures de liquides ioniques chiraux choisi pour jouer le rôle des hôtes dans ELLEs.

Une série de LIs disponibles commercialement ont été choisis pour diluer nos LIC (Figure 2-12). Cette opération a permis de sauvegarder les «précieux» hôtes chiraux, de rendre le système moins visqueux et de réduire les erreurs possibles venant de manipulation avec de petits volumes de liquides. Quand les LIs nécessaires n'étaient pas disponibles à partir des sources commerciales ils ont été synthétisés par nous-mêmes.



X= NTf_2; PF_6; BF_4
Alk= Bu, Oct
R= H; Me

Figure 2-12. LIs commerciaux choisis pour être utilisé dans ELLE.

Pour compléter le système d'ELLE l'eau a été choisi pour jouer le rôle de la deuxième phase.

Le criblage de tous les hôtes chiraux disponibles avec tous les substrats racémiques choisis a été effectué. Le système biphasique d'extraction énantiosélective a été établi par addition de liquide ionique chiral dans le liquide ionique hydrophobe commercial. La phase liquide ionique a été enrichie par le composé racémique et le système a été agité pendant plusieurs heures dans des conditions ambiantes pour laisser les molécules de l'hôte et du racémique interagir. Après cette opération l'eau a été ajoutée et le système biphasique formé a été agité pendant quelques heures supplémentaires dans le but d'extraire l'un des énantiomères (Figure 2-13).

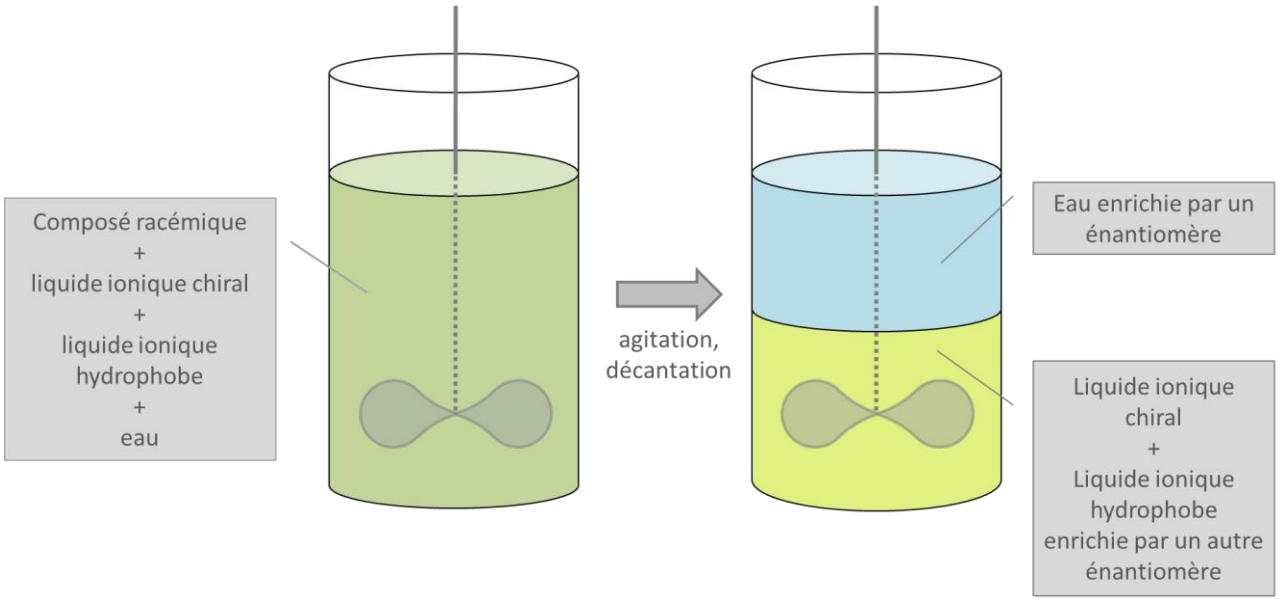


Figure 2-13. Principe du système d'ELLE.

Parmi plusieurs résultats du criblage, nous avons choisi le meilleur exemple montrant la combinaison du meilleur ee et du meilleur rendement pour continuer à étudier le rôle des paramètres importants sur le système.

Les résultats de cette recherche sont présentés dans le manuscrit ci-présent, et ont déjà donné lieu à 3 publications (qui accompagnent ce document), 6 communications orales et 8 affiches. La liste de travaux est présentée dans le chapitre 9.

3 Bibliographic part

3.1 Ionic liquids

An ionic liquid (IL) is a salt in the liquid state at low temperature. According to P. Wasserscheid, the term has been restricted to salts whose melting point is below the water boiling temperature 100 °C [12]. The most interesting are those with melting temperature below room temperature, because they allow manipulating without additional heating. These kinds of ionic liquids are called Room-Temperature Ionic Liquids (RTIL).

Generally, the structure of IL combines the presence of the head group, which generally bears the positive charge and side chains holder and counterion, neutralizing the charge of the head group (Figure 3-1).

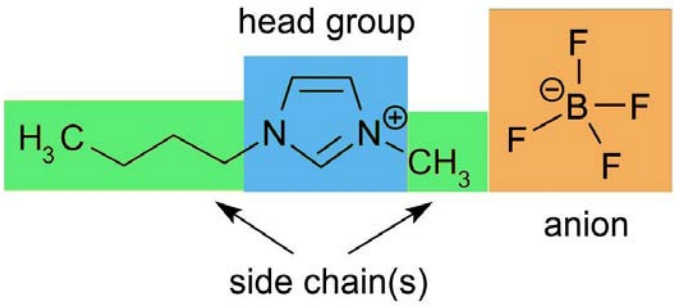


Figure 3-1. The structural elements of the ionic liquid [bmim]BF_4: head group, side chain and anion.

Ionic liquids can consist of the organic cation and inorganic anion, inorganic cation and organic anion or of both organic parts. Most commonly used cations are N,N-dialkylimidazoliums, alkylpyridiniums, alkylammoniums and the alkylphosphoniums, which are combined with various inorganic (I, Cl, Br, PF_6, NTf_2) or organic (OTf, OTs, OAc) anions (Figure 3-2).

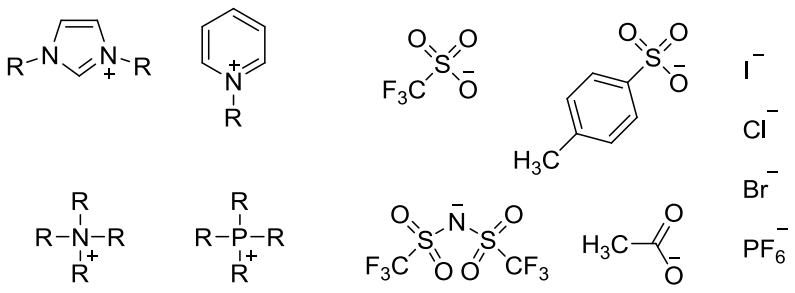


Figure 3-2. Commonly used cations and anions in ionic liquids.

In order to facilitate the understanding of the ionic liquid structure when writing, simple nomenclature has been proposed and is generally accepted in most publications. The cation is

marked in square brackets and it is named first. Common head groups have their own abbreviations: imidazolium cation is symbolized by im, pyridinium by py, ammonium by N, and the phosphonium as P. Side chains connected to the heteroatoms are symbolized by the first letter of the group (m for methyl-, e for ethyl-, b for butyl-, etc.) and are noted alphabetically on the left of the cation. The anion is noted with the chemical symbol of formula (Br, PF_6) or its abbreviation (NTf_2, OAc). Figure 1 presents the example of the IL 1-butyl-3-methylimidazolium tetrafluoroborate, or [bmim]BF_4.

The first publication concerning low-melting salt was released in 1888 by Gabriel and Weiner, who reported about ethanolammonium nitrate, which has a melting point about 52-55°C[13]. In 1914, Paul Walden received the first RTIL with a melting point below room temperature: ethylammonium nitrate $[EtNH_3]^+$ $[NO_3]^-$, which has the melting point 12°C [14]. After this publication, ionic liquids have been forgotten for a time, and were considered only as laboratory curiosities. In 1951, Hurley *et al* obtained from chloroaluminates ($AlCl_4^-$ or $Al_2Cl_7^-$) ionic liquids, which were used for electrodeposition of aluminum[15]. In 1963, Yoke *et al* reported that the mixtures of copper(I) chloride with alkylammonium chlorides are often liquid[16]. During the period from late 60s to 80s, ILs were used for the study of the kinetics of electrochemical reactions, spectroscopic and electrochemical studies of transition metal complexes[17]. In 1980, ILs were used at first as a solvent and catalyst at the same time, for the Friedel-Crafts reaction[18]. In 1990, Nobel laureate Yves Chauvin used ILs in biphasic catalysis[19]. The same year, Osteryong used ionic liquids for ethylene polymerization with the Ziegler-Natta catalyst[20]. Breakthrough in the investigation of ILs came in 1992 when Wilkes and Zavorotko, working on new electrolytes for batteries, reported[21] about the discovery of the first ionic liquids stable to air and moisture - imidazolium salts with anions BF_4^- and $MeCO_2^-$. After this event the era of active investigation of ionic liquids has been started. Number of published articles and books is constantly growing (Figure 3-3). In 2001, it was recorded more than 500 publications, in 2005 almost 1800 and 6000 in 2010 (SciFinder data). Suppliers of chemicals offer a large number of commercially available ionic liquids[22].

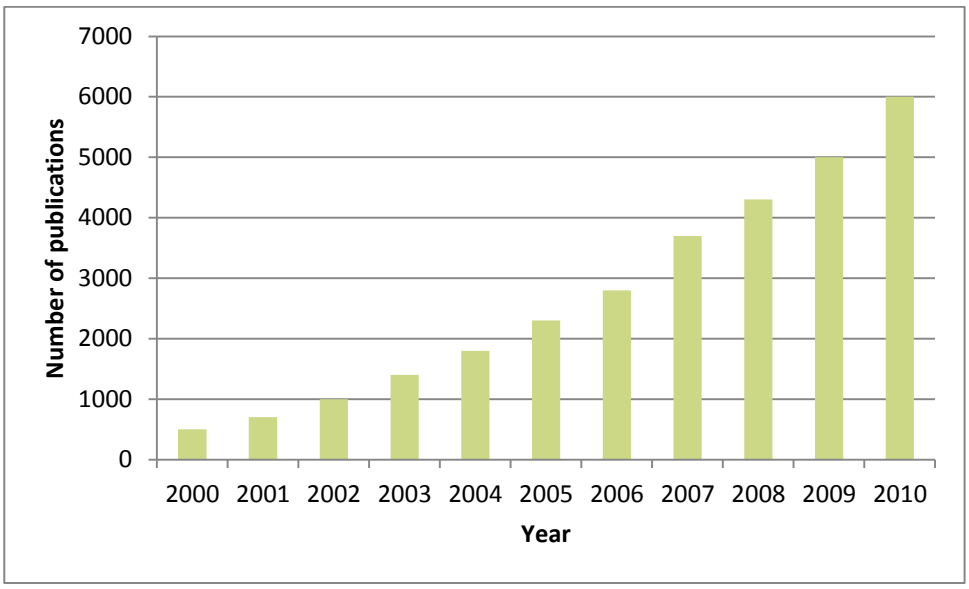


Figure 3-3. SciFinder search result for the keywords "ionic liquid" and "ionic liquids" up to Dec 2010.

Synthesis of ionic liquids consists of two main steps: the formation of the cation and anion exchange (ion metathesis). Sometimes, the second step is not required. Cation is often commercially available as halogen residue, and the anion is only needs to be replaced, to obtain the desired ionic liquid.

Formation of the cation can be achieved as a reaction with alkylation agent, resulting in quaternization of amine, phosphine or sulfide. To perform this step generally halogenalkanes or other alkylation agents are used. Quaternization reaction is quite simple - the original amine (or phosphine) is mixed with the required alkylating agent and heated while stirring, in most cases without solvent (Figure 3-4). Reaction time and temperature of heating depend on halogenalkane. Reactivity increases from chlorine to iodine. Fluorinated compounds cannot be obtained by this way.

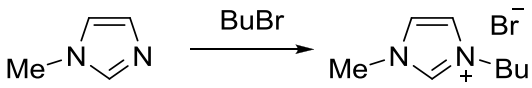


Figure 3-4. Alkylation of 1-N-methylimidazole with n-butylbromide.

The main idea of the ion metathesis reaction is the formation of a new pair of salts, which could be easily separated based on the difference in their physical properties. For example, forming a silver halide (which precipitates), or acid, or salt, which can be easily separated by washing the ionic liquid with water (only for ILs, immiscible with water). For example, the reaction of [bmim]Br with potassium hexafluorophosphate (Figure 3-5).

Figure 3-5. Metathesis of [bmim]Br with KPF_6.

The reaction forms water-immiscible ionic liquid, and the by-product, potassium bromide, stays dissolved in water.

Commonly, ILs are prepared by anion exchange of halide salts with metal salts. This method has limitations in the preparation of pure ILs due to contamination by metal halide salts. In addition, this approach is limited by the lack of suitable commercially available metal salts. Furthermore, the use of silver salts in anion exchange reactions of ILs containing amino acids is problematic due to the formation of stable silver amino acid complexes[23]. Consequently, the development of synthetic approaches to ILs based on amino acids requires that no such metal ions are employed to avoid irreversible contamination of the desired products.

Despite the ease of ILs laboratory synthesis, not all methods can be applied in industrial scale because of their high cost. Ionic liquids are positioned as "green solvents", but their production often uses large quantities of organic solvents, often for the purification of ionic liquids from halogen traces. All these shortcomings must be resolved before the transition to multiple tons synthesis. For example, the company Solvent Innovation[24] proposed, patented and manufactures in ton amounts the ionic liquid, which has the trade name ECOENG 212 (1-ethyl-3-methylimidazolium ethylsulfate). It meets all the requirements of green chemistry: it is not toxic, biodegradable, contains no halogen impurities, no solvent is used during its production, and the only byproduct is ethanol.

Since ionic liquids cannot be purified by distillation (because of near zero values of the vapor pressure), in practice the starting compounds are purified. Theoretically it is possible to distillate off any organic impurities from the ionic liquid, since many of them have good thermal stabilities and resistant to heating up to high temperatures of 400°C without decomposing. For the high-molecular-weight impurities another possibility is to clean up ionic liquids with activated carbon, following by filtration. Water usually is eliminated by heating IL for several hours at 60-80°C under reduced pressure.

In industry the possibility of ionic liquid to be simply purified for reuse is critical, because of the high cost of ILs. Efficiency varies from poor to very good[12]. Various innovative methods were proposed: extraction[25] of products with supercritical CO_2 or membrane technologies[26]. A

promising way seems to be the rent of ILs for single use from one company to another. Thus, the first one will be engaged in supplying and cleaning solvent for the second one, which will be able to save money using less expensive reusable solvent.

The interest in ionic liquids in different areas of science and technology is due to the combination of their properties. The extremely low values of their saturated vapor pressure are due to the high values of the enthalpy of evaporation of IL and make these solvents non-toxic by inhalation and not flammable. Low vapor pressure of ILs allows us to imagine new technologies, not possible to create before, like liquid mirrors for space telescopes[27]. Another remarkable property of ILs is their ability to dissolve natural polymers as cellulose, fibroin, chitin and keratin[28].

The hydrophilicity of ionic liquids can be varied depending on the desired application. It depends on the nature and size of the two constituent ions. For example, ionic liquids containing small anions like chloride, bromide or trifluoroacetate are soluble in water and are called hydrophilic. Conversely, when the anion is hexafluorophosphate or bis(trifluoromethane) sulfonate, the solubility in water is very limited, so they become hydrophobic. Many other properties of ionic liquids can be changed and adjusted "manually": melting point, acidity-basicity, viscosity, polarity, chelating properties and any others. This is the way to unlimited number of possibilities, designing special IL for any special role. This kind of ILs, created to serve specific application are called "Task-Specific Ionic Liquids" or TSIL.

The structural organization of ionic liquids is very similar to that observed in the crystalline compounds. They are the most structured liquids. In the conventional molten salts cations and anions are separated while in ionic liquids, they stay bounded by interactions[29]. The stacking of imidazolium cations in the liquid phase is described to form polymeric hydrogen-bonded supramolecules[30]. For [emim]BF_4, immediately after solidification, disorder at the anion is still observed at −54 °C, and completely ordered structure was obtained starting from −100 °C (Figure 3-6 a-b). The imidazoliums and BF_4 or PF_6 anions are linked through C–H···F interactions. The imidazolium cations display intermolecular C–H···π interactions and/or π···π stacking (Figure 3-6 c-d).

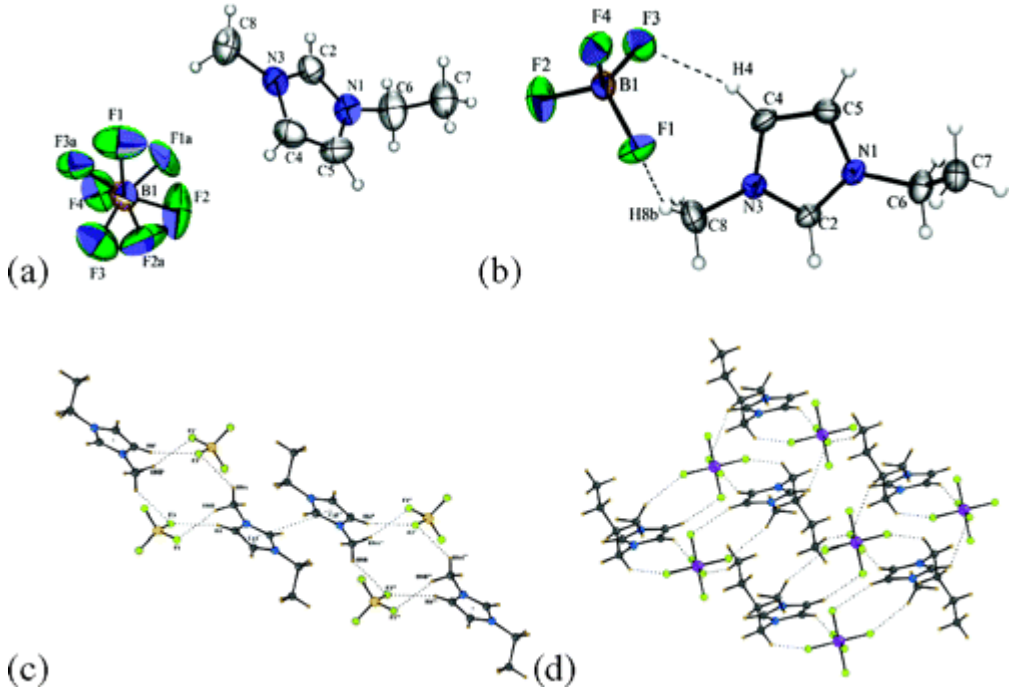


Figure 3-6. (a) [emim]BF_4 at –54 °C. (b) [emim]BF_4 at –100 °C. (c) Interionic interactions in [emim]BF_4. (d) Interionic interactions in [bmim]PF_6. Picture credit from J. Am. Chem. Soc., ***2005****, 127 (48), 16792.*

This particular property of ILs let them to dissolve a large range of compounds of all kinds, as organic, inorganic and organometallic, making ionic liquids perfect for a catalyst immobilization[31] or for applications of liquid-liquid extraction.

3.2 ILs as extraction solvents

ILs are suitable for conventional liquid-liquid extraction because of their properties, allowing them to form biphasic systems with different liquids and gases and to dissolve many different species, as organic, inorganic and biomolecules. The design of safe and environmentally benign separation processes plays an increasingly important role in the development of extraction technology. ILs seem to be the best candidate among other greener equivalents for conventional organic solvents not because their solution or physical properties viewed separately, but unique combinations of their properties taken together.

Known applications of ionic liquids in sample preparation include liquid–liquid extraction, aqueous biphasic systems, extractive distillation, liquid-phase microextraction, micellar extraction, matrix solvents for headspace analysis, and supported liquid membrane extraction.

Among extraction targets are examples of almost all classes of organic compounds, inorganic ions and large biopolymers. The objective of extraction can be separation of desired product (like rare earth elements[32], alkaloids, drugs, proteins, etc.) or purification of substrate from undesired impurities (like Hg, Cd, polycyclic aromatic compounds, etc.). Extraction of organic compounds[33], biomolecules[34] and applications of ILs in separation technology[35] were very recently reviewed.

In this work we were particularly interested in the extraction of amino acids and their derivatives. First example of amino acids extraction to ILs was published by Armstrong's group in 2003[36]. The ionic liquid/water distribution coefficients were measured using liquid chromatography amino acids and for a set organic compounds with various functionalities. The distribution coefficient in the [bmim]PF_6 for amino acids histidine, phenylalanine, and tryptophan were low; the $P_{IL/water}$ values at pH 5.1 were 0.17, 0.013, and 0.012 respectively (Table 3-1). The distribution coefficients at pH 2 and pH 10 were so low that they could not be measured accurately. Only the aromatic amino acids were measured because the solute concentration in both phases was determined using HPLC peak areas at 254 nm UV absorbing.

Amino acid	$P_{[bmim]PF_6/water}$		
	pH=2	pH=5.1	pH=10
His	-	0.17	-
Phe	-	0.013	-
Trp	-	0.012	-

Table 3-1. Distribution coefficients of His, Phe and Trp at different pH between [bmim]PF_6/water.

However, it was possible to extract AAs partially by adding a crown ether to the ionic liquid phase and working at pH 1. The positive form of amino acids is complexed by the crown ether and the complex is extracted in the ionic liquid phase. The apparent distribution of phenylalanine and tryptophan were 0.41 and 1.7 at pH 1.0 respectively. These values are two orders of magnitude higher than the corresponding values without crown ether.

This observation was confirmed in 2004 by Smirnova *et al*[37]. High extraction efficiency of amino acids by [bmim]PF_6 was observed in the presence of the crown ether dicyclohexano-18-crown-6 (Figure 3-7), but the extraction rate was rather low without it. To explain this observation an ion exchange mechanism was proposed and confirmed by the studies of pH. The mechanism requires an optimum pH and involves the binding of an ammonium group on the amino acid to

the dicyclohexano-18-crown-6 ether. The extraction of tryptophan, leucine, alanine, glycine, arginine and lysine from water was nearly quantitative in the above mentioned system.

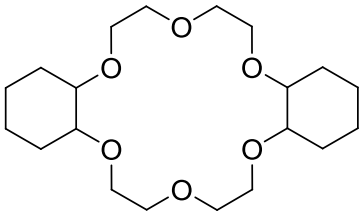


Figure 3-7. Dicyclohexano-18-crown-6 used as host in amino acids extractions to [bmim]PF_6.

One year later Wang *et al.* studied the extraction of the amino acids using the ionic liquids [bmim]PF_6, [hmim]PF_6, [hmim]BF_4 and [omim]BF_4 from aqueous solution of valine, leucine, tyrosine, phenylalanine, and tryptophan[38]. The partition coefficients for the aromatic amino acids were higher than for the aliphatic amino acids and were in the range of 0.005–10. For all ionic liquids the partition coefficients were shown to be a function of pH: they are small in the range of pH<pK_{a1}, and reach maximum values for pK_{a1}<pH<pK_{a2}. Two main factors responsible for the extraction efficiency by the ionic liquids are the hydrophobicity of the amino acid (which increase near the isoelectric point) and the force of electrostatic interactions between the amino acids and the ionic liquids (amino acids with polar functional groups tend to exhibit smaller partition coefficients). Interesting to note, that ILs containing a BF_4 anion exhibit higher extraction efficiency than ionic liquids containing the PF_6 anion. This can be explained by the presence of the stronger effective charge on the BF_4 anion. Increasing the alkyl chain length of the IL cation resulted in a decrease of the partition coefficient. Also, no correlation was found between the polarity of the tested ILs and the partition coefficients.

At the beginning of this work, the above-mentioned papers were the only examples of AAs non-enantioselective extraction using ILs. A lot of new information concerning this area of research was published during last 3 years.

Investigations of molecular-level mechanisms which influence the behavior of aqueous solutions of salts and ILs were provided in the recent work of Coutinho and coll.[39]. It was found that the influence of inorganic anions on the liquid-liquid behavior of [bmim]$C(CN)_3$ and water qualitatively respects the Hofmeister series (or lyotropic series, which is a classification of ions in order of their ability to salt out or salt in proteins). The proposed model explains the salting-out and salting-in effects to be dependent on the nature and concentration of the ions and can

be understood like water-mediated direct or indirect interactions between the anions and the solute, and not like the changes in the water structure stimulated by the inorganic ions.

The nature of the salting-out and salting-in phenomena is explained to be essentially different and related to two major specific ion effects (Figure 3-8):

1) salting-in is promoted by a direct binding between the ions of low charge density and the hydrophobic moiety of the IL;

2) salting-out is originating by an entropically driven effect, related to the formation of hydrated complexes away from the solute hydrophobic parts and to an increasing on the surface tension of water and thus on the energy of cavity formation, due to the presence of high charge density ions.

In continuation of previous work, the influence of a series of 12 amino acids on the liquid-liquid equilibria between partially miscible [bmim]$C(CN)_3$ and water was studied to evaluate the possible interactions between these compounds[40]. Observed solubility effects were dependent on the polarity, size, and charge distribution of the amino acid side chains and are explained in terms of the model described above for specific ion effects on aqueous solutions of imidazolium-based ILs. The salting-out phenomenon takes place when hydration is preferential, and it happens with hydrophilic amino acids which have no or have short alkyl chains. While increasing the number of nonpolar groups, the interaction with the IL cation hydrophobic moieties becomes more important and shifts the existing interactions with water, decreasing the observed solubility. The salting-in effect is induced when the side chain of the AA is hydrophobic. Hydrophilic amino acids are able to form hydration complexes, thus resulting in a decreasing of IL and water mutual solubilities (Figure 3-8).

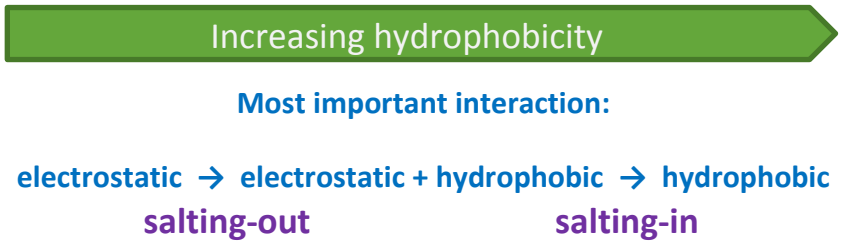


Figure 3-8. The origin of salting-in and salting-out effects.

Observed phenomena proof the influence of amino acids on the solubility of IL. The salting-in/-out effects can be explained as delicate balance differencing direct or indirect water-promoted interactions between the amino acids and the solute. These interactions are determined by the

attractions of the AA side chains to water and/or to IL ions and they are dependent on their polarity, size, and charge. Combination of these properties possesses the permanent competition of the interaction/repulsion between all participants in the solution. The delicate balance between these interactions is dependent on the relative affinities of the AAs to water molecules or to IL cation and/or anion and determines the trend and magnitude of the solubility effect observed.

In 2010, was published the complete study of the tryptophan extraction using hydrophobic ionic liquids[41]. Extractions were carried out from aqueous solutions into 17 hydrophobic ILs, selected in order to evaluate the attraction of IL anions and cations, alkyl side chain length and polarity of the IL on the recovery of the amino acid between the two phases. The pH dependence of the partition coefficients was evaluated also. Determined factors, on which the partition coefficients are dependent, are: the pH of the aqueous phase, the nature of the anion of the IL and the chemical structure of the IL cation. In the range $pH<pK_1$ the more efficient extractions were obtained with ILs containing BF_4^- anion. Increasing the length of the alkyl side chain and increasing the number of substitutions at the IL cation decreases the ILs extraction ability for Trp. The degree of extraction is decreasing the next order: pyrrolidinium > imidazolium > pyridinium > piperidinium based ILs. This finding order suggests that besides the obvious electrostatic interactions between the cationic form of Trp and the IL anion, a complex of other important interactions plays a role on the level of the amino acid phase preference.
Collected information highlights the suitability of NTf_2–based hydrophobic ILs/water mixtures as liquid–liquid extraction systems. Despite of the good results obtained for BF_4–based ILs, they are not recommended for the extraction of biomolecules from aqueous media and particularly from acidic one. This can be explained from a practical point of view, because of their low stability to those conditions.
Two possible mechanisms of the molecule transfer play the role in the extraction process of AAs: simple dissolving of amino acids and ion exchange. Electroneutrality requires that if the amino acid transfers to the ionic liquid phase as a cation, an equal amount of IL cations must enter the aqueous phase. That is why the ion-exchange processes play a significant role in the mechanism of phase transfer and are determinant while interpreting the behavior of IL/AA systems at different pH values.

All reported results show the fast increase of interest during last 3 years to utilization of ILs as extraction solvents. ILs were shown to be effective and suitable solvents of new generation and

they thus might be used for the optimization of biochemical recovery and purification procedures through the manipulation of the experimental conditions and the development of new ILs that can meet the requirements of any particular task. But before their utilization in real-world industrial applications some questions are still to be answered. For example, ionic liquids with NTf_2 anion are reported to be hydrophobic, and it was found that their solubilities in water are small but not negligible. This small aqueous solubility of hydrophobic ionic liquids affects interfacial properties and hence use of these compounds in liquid-liquid separations[42]. That is why the search for novel types of more ecofriendly ILs is still ongoing. One possible approach consists of reducing the toxicity of ILs is the application of natural products like amino acids or sugars for IL synthesis.

Those ILs can be chiral, thus opening the way for more specific applications. Their role during extractions can not be limited only to dissolution of extracted species, but to enantiomeric interactions between CIL and solute, making possible selective extractions of enantiomers. This kind of extraction will be called Enantioselective Liquid-Liquid Extraction (ELLE).

3.3 Chiral ionic liquids

Chiral ionic liquids (CILs) may have their chirality origin from any type of chirality. Usually it is central, but can be axial or planar. Additionally, it can be found in both cation, and the anion – the so called doubly chiral IL.

The first CIL, an imidazolium salt with a lactate as chiral anion, was published by Seddon in 1999[43], and in the following years most of the CILs had chiral cations derived from the "chiral pool". As a consequence of the great acceptance of ILs as potentially green solvents, much attention was given to the synthesis of CILs from chiral biomolecules. Among others, there are described examples of CILs from alkaloids, terpenes, amino acids, etc.[44] (Figure 3-9).

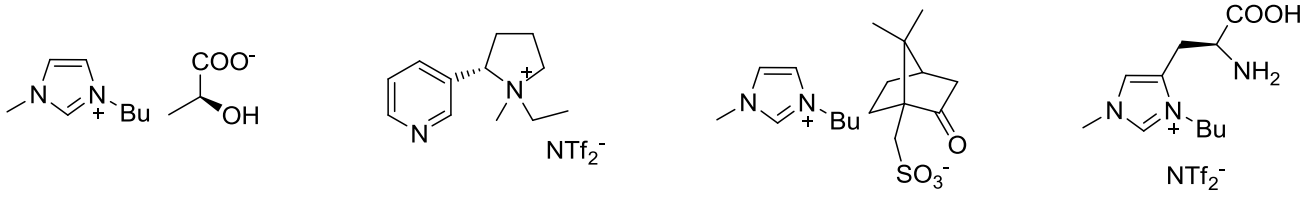


Figure 3-9. Examples of chiral ionic liquids derived from bioresources.

Great number of CILs is already described, and the possible quantity of structures is virtually infinite. Some of them are available commercially already[45].

Despite the rapid design of new CILs, no successful applications were known for some time. In fact, it took nine years after the first publication of CIL, that a highly enantioselective synthesis with an enantiomeric excess more than 90% was reported[46].

Nevertheless, this field is growing rapidly, and the majority of applications can be divided into three different groups:

- Asymmetric synthesis applications
- Spectroscopic applications
- Chromatographic applications

Brief history of CILs, their preparation and application as a reaction media and chiral reagents can be found in the book chapter "*Chiral ionic liquids for asymmetric reactions*"[47] edited by our team.

The last two applications of CILs are based on another property of CILs: chiral recognition, which was the major interest of our research. This means the preferential interaction (discrimination) of one enantiomer to another. Because of a very well organized 3D structure, CILs have an intrinsic potential for enantioselective recognition, especially because in a well-organized media it is reasonable to expect some chiral interactions. The chiral recognition using CILs for enantioselective recognition may take place through the combination or solitary effect of non-covalent interactions as ion-pairing formation, hydrogen bonding, Van der Waals forces, dipole-dipole interaction, etc.

3.3.1 Spectroscopic applications

The presence of chiral recognition in CIL media was proved by spectroscopic applications. The first example of the NMR application of CILs was published in 2002 by Wasserscheid *et al*., who showed that CILs can be used for the determination of enantiomeric excess of samples by ^{19}F NMR peaks integration[48]. Ephedrine-based CIL was mixed with racemic Mosher's acid sodium salt in order to investigate diastereomeric interionic interactions between the enantiopure CIL and a racemic substrate (Figure 3-10). A splitting of the ^{19}F signal of the CF_3 group was observed to be dependent on the ratio of CIL used in the experiment, thus confirming the

presence of chiral environment. A minimum concentration of 0.3 mmol/mL of CIL was observed to be necessary to achieve sufficient resolution by the chemical shift difference. Interesting to note that in the presence of catalytic amounts of water a significant enhancement of splitting was observed.

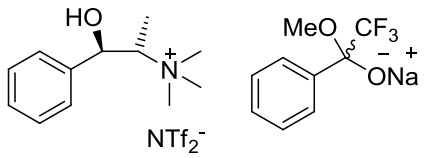


Figure 3-10. Ephedrine-based CIL with racemic Mosher's acid sodium salt used the determination of ee by ^{19}F NMR.

The group of A.-C. Gaumont extended the method experiment with chiral thiazolinium salts and obtained a good splitting of signals[49] (Figure 3-11). It was shown the importance of an aromatic group presence for π-π stacking interactions between the racemic compound and the CIL. When in the thiazolinium CIL the corresponding N-phenyl was replaced by N-ethyl, considerably weaker interactions were observed.

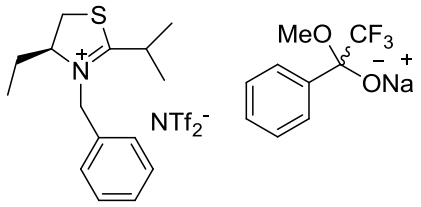


Figure 3-11. Thiazolinium-based CIL with racemic Mosher's acid sodium salt used the determination of ee by ^{19}F NMR.

The best result for the moment in splitting ^{19}F NMR signal was 152 Hz, when unusual boron-containing anion was used[50] (Figure 3-12). Important to note, that when the BF_4^- salt was applied, no interactions were observed, thus proving the strong influence of the anion. The presence of a second diastereomeric interaction site as the hydroxy group improved the recognition also.

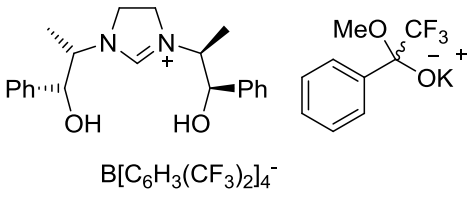


Figure 3-12. The best example of splitting the ^{19}F NMR signal of Mosher's acid salt by CIL.

Chiral recognition in ^{1}H NMR spectroscopy was reported in literature also. But remarkably few CILs show it, since a significant splitting of signals is much more difficult to obtain in comparison to ^{19}F NMR spectroscopy. The highest splitting in ^{1}H NMR spectroscopy up to 60 Hz was reported by Clavier et al. using the CIL derived from the (*S*)-valine[51] (Figure 3-13). To make possible two different kinds of interactions two different groups were introduced: from the one side of the molecule phenyl group with an additional *t*-butyl substituent in ortho position and the hydroxyethyl substituent was introduced from the other side. Also, 1 mole of crown ether 18C6 was added and potassium cation in the Mosher's acid salt instead of sodium. The improvement of interactions can be explained by the tightness of the anion pair in the presence of a bulky counter cation like potassium that is trapped by the crown ether 18C6.

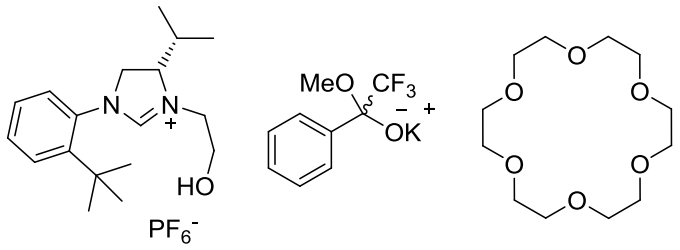


Figure 3-13. The best example of splitting the ^{1}H NMR signal of Mosher's acid salt by CIL.

Numerous examples confirming the presence of chiral recognition in CIL media determined by NMR spectroscopy were published from the first report in 2002. All known examples were reviewed recently by Bica and Gaertner[52].

Not only NMR technique was used for observing chiral discrimination in CIL media. A method in which a CIL was used for the determination of enantiomeric purity based on near-infrared techniques was developed by the group of Oliveira[53]. Different pharmaceutical products and amino acids were dissolved in the CIL to visualize diastereomeric interactions in NIR spectroscopy (Figure 3-14). Multivariate data analysis resolves the enantiomeric composition of samples of the medicament atenolol in high sensitivity of microgram scale and accuracy of ee as low as 0.6 %. The same CIL was used for chiral recognition agent and solvent for the determination of enantiomeric excess of different drugs through fluorescence spectroscopy. This method was proved to be superior to other methods including HPLC, GC, NMR and FTIR in terms of accuracy, sensitivity and time of analysis.

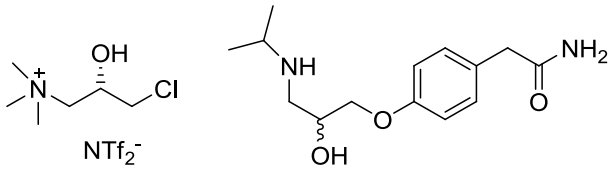


Figure 3-14. The pair atenolol – CIL used in NIR analyses.

3.3.2 Chromatographic Applications

Another major field of utilization of chiral recognition property of CILs is chromatography. It can be divided into two major fields of application: the use of CILs as stationary phases for chromatography and utilization in capillary electrophoresis.

Alkylimidazolium-based ILs were successfully used as stationary phases for gas chromatography and showed unusual stability. Their dual nature properties let them separate both polar and non-polar compounds[54]. They are two principal ways of their utilization in chromatography: dissolving a chiral selector in a non-chiral IL, or more elegant way when the IL is chiral itself[55].

The first direct enantiomeric separation of different compounds by using CIL stationary phases in gas chromatography was published by the group of Armstrong in 2004 [56]. To generate a new chiral stationary phase (CSP) the N,N-dimethylephedrinium-based CIL (Figure 3-15) was coated on fused-silica capillary column with a brown polyimide layer. A range of chiral compounds such as alcohols, diols, sulfoxides, epoxides and acetamides were proven to be be successfully separated. Utilization of natural molecule as ephedrine, which is present in nature in both enantiomeric forms and as diastereomeric pseudoephedrine, rendered possible to produce CSPs of opposite stereochemistry, which reverses the order of enantiomeric elution of the analytes. This is very difficult to do with routinely commonly used chiral selectors in GC or LC like the popular cyclodextrin CSPs.

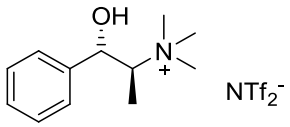


Figure 3-15. (1S,2R)-(+)-N,N-dimethylephedrinium bis(trifluoromethylsulfonyl)amide used to coate the capillary column.

Capillary zone electrophoresis is a very useful separation technique with high performance for separation of small charged molecules or for the separation of peptides, proteins or fragments

of nucleic acids. In the last years ILs were studied to be used as new media for capillary electrophoresis with IL-containing background electrolytes[57]. New IL-type surfactants and their polymers were used first time for chiral separation of acidic analytes in micellar electrokinetic chromatography in 2006 by Shamsi and coll[58]. Two CILs were prepared from amino acids and were used as pseudo-stationary phase in capillary electrophoresis as well as their polymers (Figure 3-16). It was shown that chiral separation is dependent on the presence of opposite charge and on the nature of substituents (compatibility between chiral selector and analyte).

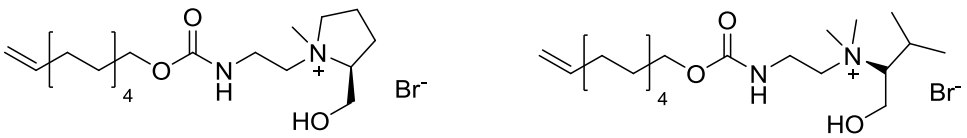


Figure 3-16. CILs used in capillary electrophoresis.

Other known examples of chromatography application of CILs were reviewed in 2008 by Bica and Gaertner[52].

All mentioned above applications of CILs like in asymmetric synthesis, spectroscopic and chromatographic techniques prove the chiral recognition property of CILs to discriminate one enantiomer to another. This is the good stimulus to continue the search for new efficient, simple and cost-effective applications of CILs in preparation of pure enantiomers.

We focalized our attention on several classes of chiral compounds, as starting material for preparation of our CILs: (*S*)-histidine, (1*S*,2*S*)-diaminocyclohexane and (*R*,*R*)-tartaric acid.

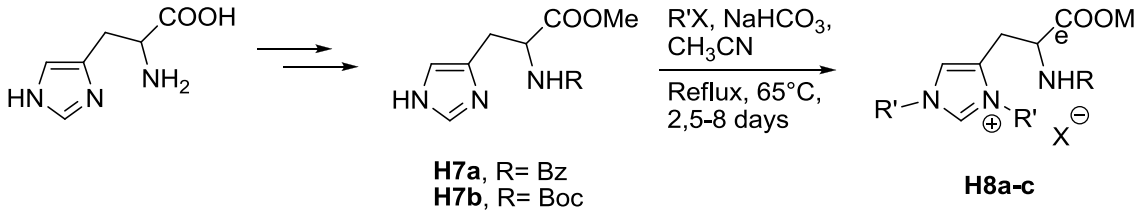
3.4 Histidinium-based ionic liquids

One of the main priorities of modern organic chemistry is fabrication and application of new solvents, meeting the goals of green chemistry and having useful properties in the same time. To prepare this kind of materials, α-amino acids are the prominent series of starting material. They are widely available at low cost and give us great molecular diversity from which could be built a large variety of structures. All natural amino acids can be used as chiral pools to give chiral ionic liquids in simple and efficient way[59].

One natural amino acid, (*S*)-histidine, is of particular interest to the chemistry of ionic liquids because of its structure, containing imidazolium ring. Greater part of commercially available ionic liquids contain imidazolium core[12]. Imidazolium cation part can be modified by varying

the substituent on intracyclic nitrogen atoms without touching the part of the amino acid. That is why the combination of chiral amino acid part with imidazolium part is a good way to the chiral bifunctional ionic liquids[60].

In 2005, Erker and co-workers were first to prepare histidine-based chiral ionic liquids[61]. Acidic function of L-histidine was protected by formation of methyl ester and then amine function was protected with benzoyl or Boc to give the compounds **H7a** and **H7b** (Figure 3-17). Alkylation of **H7a** histidine derivative with n-propyl bromide or isopropyl iodide under basic conditions in acetonitrile at reflux for several days gave ionic liquids **H8a** and **H8b**, respectively. Ionic liquids **H8c** and **d** were obtained similarly from histidine derivative **H7b**. Obtained ionic liquids have melting points in the range 39–55 °C and high water solubility.



H8	R	R'	X	Yield, %
a	Bz	*n*-Pr	Br	72
b	Bz	*i*-Pr	I	95
c	Boc	*n*-Pr	Br	92
d	Boc	*i*-Pr	I	69

Figure 3-17. Erker's synthesis of histidinium-based ionic liquids.

A year later, Guillen et al. used histidine as the starting material in the synthesis of a new series of imidazolium ionic liquids, in which two nitrogen atoms of imidazolium unit of histidine were alkylated with different alkyl chains[62]. Desymmetrization of imidazolium cation lowers the melting point because the asymmetry of the cation creates a distortion of the crystal mesh, leading to a decrease in melting temperature. Chiral amino acid unit of (*S*)-histidine after all reactions remained unchanged. Protection of histidine methyl ester via a cyclic urea structure, followed by alkylation with iodomethane and opening of the cyclic urea by *t*-BuOH in the presence of $(i\text{-Pr})_2$NEt, gave histidine derivative **H2**. Alkylation of **H2** with bromobutane followed by anion metathesis resulted in ionic liquids **H9a–c** in 65–90% yields (Figure 3-18).

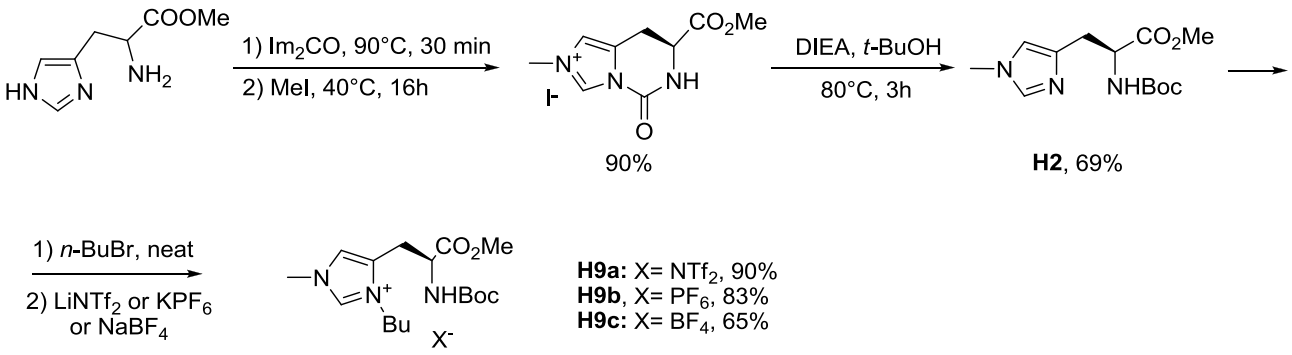


Figure 3-18. Synthesis of bis-protected histidinium salts.

Compound **H9a** melt at 40°C and have a good thermal stability up to 170°C[63]. Salts **H9b** and **H9c** are real ionic liquids with low glass transition points: they have glass transition temperatures of -38°C and -29.4°C, respectively[64].

Compound **H9a** was deprotected selectively by N- or O- positions, or by both amino acid functions, afforded various ionic liquids **H10-H12** (Figure 3-19).

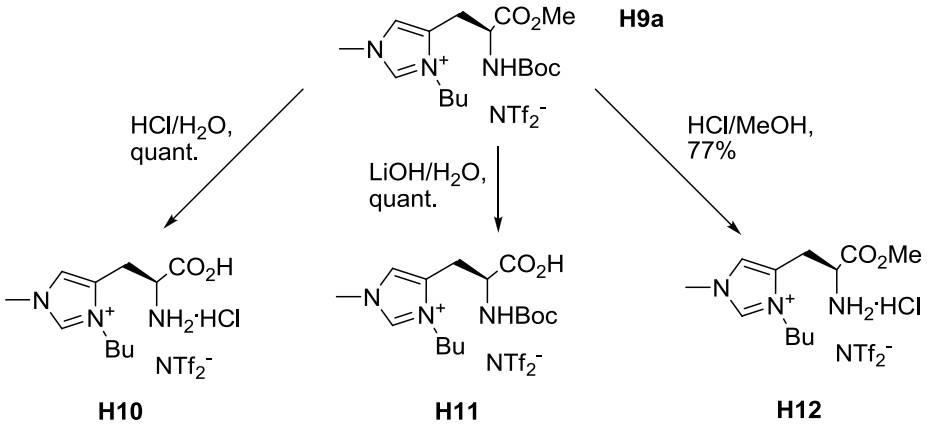
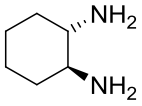


*Figure 3-19. Selective or complete deprotection of **H9a**.*

Histidinium amino acid derivatives were introduced to peptidic coupling with alanine derivatives at either N- or C-terminal position affording dipeptides in good yield. Only one diastereoisomer of each dipeptide was obtained, confirming that no racemization occurred during the series of synthetic steps.

3.5 1,2-diaminocyclohexane based compounds

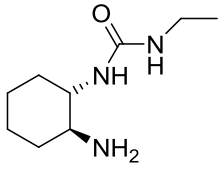
S,S enantiomer of 1,2-diaminocyclohexane ((*S,S*)DACH) (Figure 3-20) is commonly used in modern chemistry[11]. Indeed, its structural part is widespread in resolving reagents[65], chiral reagents[66], chiral ligands[67] or the key component for drugs synthesis[68].



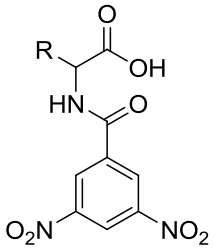
$C_6H_{14}N_2$
M_W 114.2
CAS: 21436-03-3

Figure 3-20. (1S,2S)-diaminocyclohexane

For resolving purposes (1*S*,2*S*)-diaminocyclohexane shows good efficiency. Compound **D1** was used as an NMR chiral solvating agent for the determination of the enantiomeric composition of N-(3,5-dinitrobenzoyl)-α-amino acids[69] (Figure 3-21). Even when it contains only primary amino group and an ureide group, the 1H NMR chemical shifts for the protons on the 3,5-dinitrophenyl ring of N-(3,5-dinitrobenzoyl)-α-amino acids were always greater than 0.037 ppm. This is good enough to be utilized for determination of the enantiomeric composition.



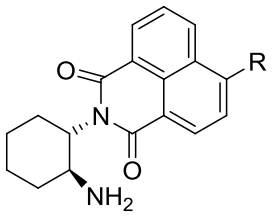
D1



R= aminoacid side chain

Figure 3-21. (1S,2S)-diaminocyclohexane-based chiral solvating agent and resolved N-(3,5-dinitrobenzoyl)-α-amino acid.

Chiral solvating agents derived from optically active trans-1,2-diaminocyclohexane were utilized for the determination of enantiomeric composition of chiral compounds containing one or more aromatic functional groups. Compounds **D2** derived from (1*R*,2*R*)-1,2-diaminocyclohexane (Figure 3-22) were successfully applied to the determination of enantiomeric composition of chiral carboxylic acids by NMR spectroscopy[70].

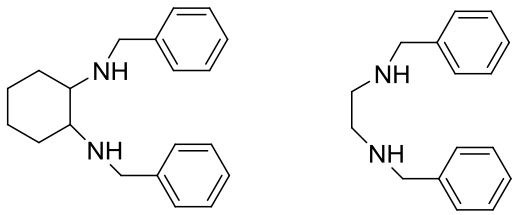


D2 R= H; Br; $N(CH_3)_2$

Figure 3-22. (1R,2R)-1,2-diaminocyclohexane-based chiral solvating agents containing aromatic parts.

These chiral solvating agents were designed to contain aromatic functional groups in order to induce magnetic anisotropic influence and to invoke π-π interaction with analyzed compounds. Most chiral solvating agents, which were developed and utilized with success in the determination of the enantiomeric composition of chiral compounds by NMR spectroscopy, containing one or several aromatic functional groups to induce magnetic anisotropic influence and to invoke π-π interaction with analyzed compounds[69].

Compound **D3** is the structural analogue of benzathine (Figure 3-23), a widespread diamine, used as a component in some medications including benzathine phenoxymethylpenicillin and benzathine benzylpenicillin. It stabilises penicillin and prolongs it sojourn when injected into tissues[71].

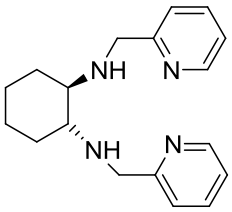


D3 Benzathine

*Figure 3-23. N^1,N^2-bis(benzyl)cyclohexane-1,2-diamine **D3** and Benzathine.*

Compound **D3** is widely used in different applications. Among other applications, it was used as ligand[72], potential anticancer agent[73] and for circular dichroism studies[74].

Another application of *trans*-1,2-diaminocyclohexane containing aromatic functional groups is preparation of chiral metal complexes. A lot of examples of use symmetrical bis-(pyridin-2-ylmethyl) substituted (1*R*,2*R*)-diaminocyclohexane **D2,2(*R,R*)** (Figure 3-24) are known. First time it was prepared in 1984 by Goodwin *et al.* and was used for synthesis of chiral complexes of Co (III)[75]. Among other applications, synthesis of manganese(III, IV)[76], cobalt(II)[77] or palladium[78] complexes.



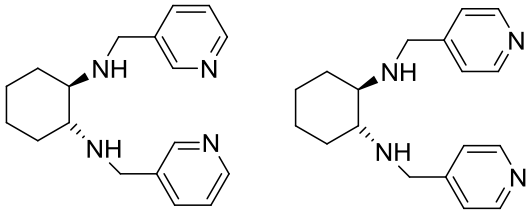
D2,2(*R*,*R*)

Figure 3-24. (1R,2R)-N¹,N²-bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine.

Chiral complexes of manganese with **D2,2(*R*,*R*)** compound were successfully used in the catalytic epoxidation of terminal olefins[79]. Copper (II) complexes of **D2,2(*R*,*R*)** compound catalyze Henry and aza-Henry reactions high yield and good enantioselectivity[80].

(*S*,*S*)-enantiomer of compound **D2,2** was also successfully used in preparation of ruthenium and iron-based chiral complexes which were used as catalysts for the oxidation reactions[81]. Manganese complexes of **D2,2(*S*,*S*)** were found to catalyze enantioselective olefin oxidation to the corresponding epoxides with different oxidants[82].

One example of synthesis and application of compound's **D2,2(*R*,*R*)** homologues: **D3,3(*R*,*R*)** and **D4,4(*R*,*R*)** is known (Figure 3-25). They form supramolecular complexes with copper (II) and was shown to be good catalysts for Henry and aza-Henry reactions[80]. These compounds were unknown at the beginning of our work.



D3,3(*R*,*R*) **D4,4(*R*,*R*)**

Figure 3-25. Pyridin-3 and pyridin-4 -ylmethyl (R,R)DACH-based compounds.

All methods of synthesis of compounds **D2,2(*R*,*R*), D3,3(*R*,*R*)**, **D4,4(*R*,*R*)** or their (*S*,*S*)-antipodes are based on formation of Schiff base between corresponding benzaldehyde or pyridinecarboxaldehyde and *trans*-(1,2)-diaminocyclohexane followed by reduction of imine (Figure 3-26).

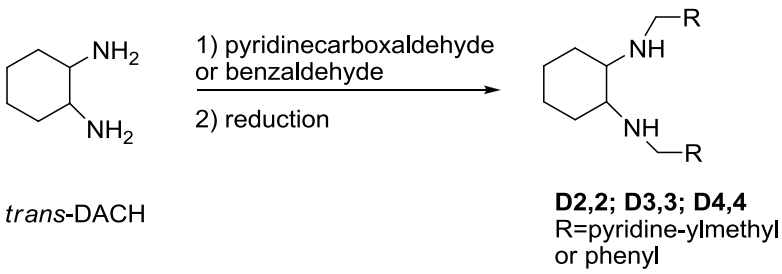
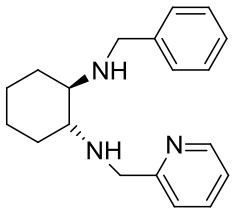


*Figure 3-26. Synthesis of symmetric compounds **D2,2; D3,3** and **D4,4**.*

Symmetrical aryl- and heterocyclyl-substituted *trans*-DACH compounds showed inhibitory activity against human MCF-7 breast cancer cells and were patented in 2008 by Chinese group[83].

One example of synthesis and application of dissymmetrical benzyl and 2-pyridyl substituted (1*R*,2*R*)-1,2-diaminocyclohexane is known. A number of complexes of the type [Co(R,R-diamine)(dipeptidato)]$^{+}$, where R,R-diamine is dissymmetrical (1*R*,2*R*)-diaminocyclohexane derivative (Figure 3-27) and dipeptidato is the amino acid dianion, were synthesized and characterized[84].



D4,Ph(*R*,*R*)

Figure 3-27. (1R,2R)-N1-benzyl-N2-(pyridin-2-ylmethyl)-cyclohexane-1,2-diamine, used for preparation of chiral metal complexes.

Compound **D4,Ph(*R*,*R*)** was prepared by repeating two times the same experimental mode with two different aldehydes. First, imine formation was performed by reaction of (1*R*,2*R*)-diaminocyclohexane with one equivalent of pyridine-2-carboxaldehyde followed by hydrogenation over 10% Pd on carbon. After purification by vacuum distillation the resulting (1*R*,2*R*)-N^{1}-(pyridin-2-ylmethyl)cyclohexane-1,2-diamine **D0,2(*R*,*R*)** was introduced to the same procedure with benzaldehyde giving final product **D4,Ph(*R*,*R*)** with 66% overall yield (Figure 3-28).

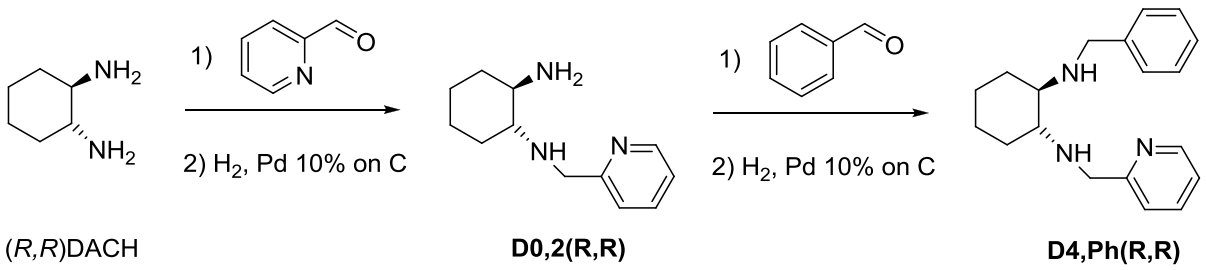


Figure 3-28. Preparation of dissymmetrical (1R,2R)-diaminocyclohexane derivaty.

Preparation method for N-monosubstituted trans-1,2-diaminocyclohexane derivatives (compound **D0,2(*R,R*)** and its homologues) was covered in 2010 by patent[85]. (1*R*,2*R*)-cyclohexanediamine was reacted with $(Boc)_2O$ to obtain mono-protected intermediate, followed by reaction with corresponding aldehyde at room temperature for 20 min, reduced with $NaBH_4$, and addition of 4M HCl in EtOAc to give corresponding (1*R*,2*R*)-N-substituted 1,2-diaminocyclohexane dihydrochloride (Figure 3-29).

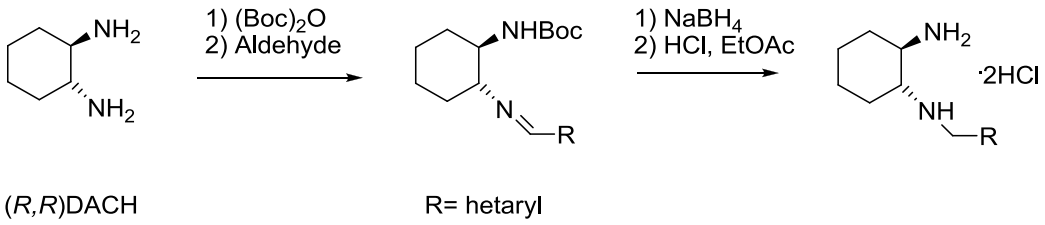


Figure 3-29. Preparation of N-monosubstituted trans-1,2-diaminocyclohexane derivatives.

In 2008 was reported about the successful use of (*R,R*)-DACH cobalt(III) complex for the extraction of one enantiomer into an organic phase by selective coordination to the DACH hydrophobic selector[86]. Racemic *N*-benzyl α-amino acids (*N*-Bn-AA) has been resolved by a liquid-liquid extraction process: one enantiomer (*S*) of the *N*-benzyl α-amino acid predominated in the aqueous phase, while the other enantiomer (*R*) was driven into the organic phase by the complexation with cobalt (Figure 3-30). For more details on this example see Figure 3-49.

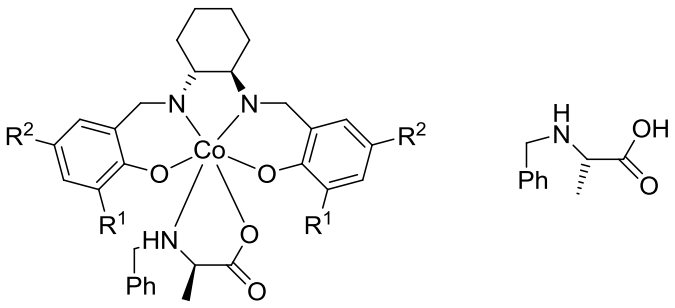


Figure 3-30. Chiral cobalt host and resolved alanine derivative.

3.6 Tartaric acid-based compounds

The main target of the search for new CIL is the synthesis of functionalized CIL which may work as task-specific compounds. Taking in account that ionic liquids are accepted as green solvents, particularly interesting are those obtained from renewable sources rather than from compounds derived from petroleum. In this context, new CIL from the natural chiral compounds constitute as a low cost and sustainable ones.

Tartaric acid occurs naturally in many plants, particularly grapes, bananas, and tamarinds, and is one of the main acids found in wine. The naturally occurring form of the acid is (*R,R*)-tartaric acid or L-(+)-tartaric acid or dextrotartaric acid (Figure 3-31). As a food additive, tartaric acid is used as an antioxidant with E number E334, tartrates are other additives serving as antioxidants or emulsifiers.

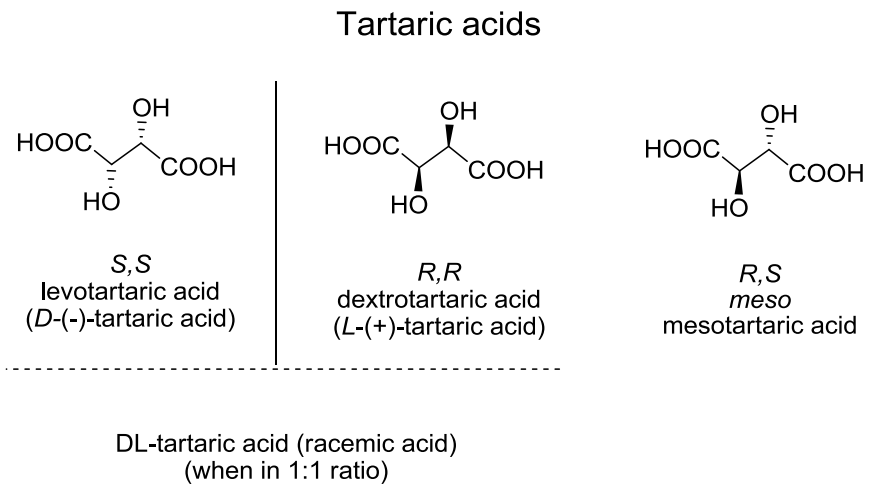


Figure 3-31. Family of tartaric acids.

First example of CILs, based on tartaric acid, was published in 2006 by Masters and coll. A large range of tetrabutylammonium salts were obtained from (*S,S*)- and (*R,R*)- tartaric acids[87] (Figure 3-32). A 40% w/w aqueous solution of tetrabutylammonium hydroxide was added to an aqueous suspension of the tartaric acid. The resulting mixture was heated at 60°C for 2 hours. The water was evaporated in vacuo at 80°C. To remove the unreacted acid the resultant compound was dissolved in CH_3CN and filtered. The filtrate was dried over Na_2SO_4, filtered and the solvent was removed in vacuo to afford the final product.

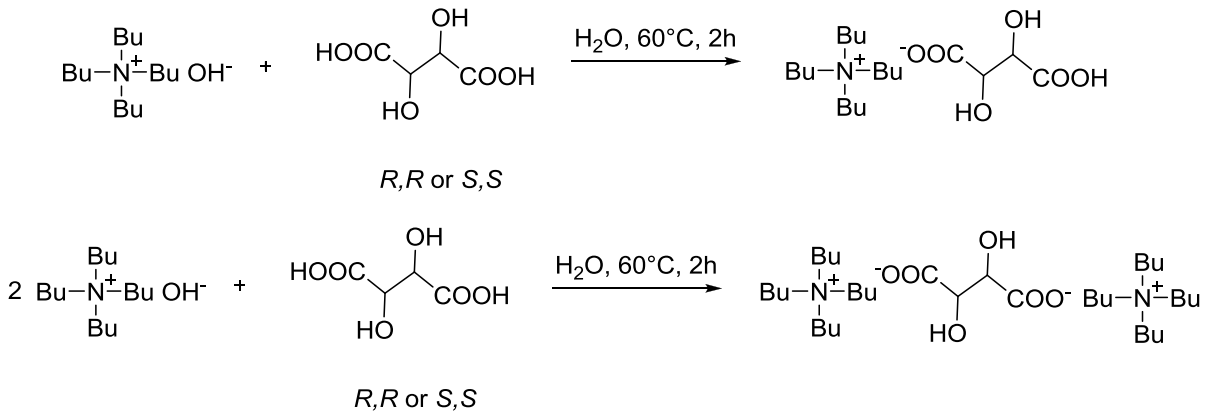


Figure 3-32. Synthesis of CILs from tetrabutylammonium hydroxide and tartaric acid.

Tetrabutylammonium hydroxide, [TBA]OH, is a strong base, which effectively deprotonates the carboxylic acid part of amino acids and organic acids to form a carboxylate salt and water. Tetrabutylammonium cation decreases intermolecular attractions because of its bulky nature, thus maximizing the probability of the resulting salt being a liquid at room temperature. Interesting to note, that clear shifts of the α-protons in the starting acid and the resulted CILs were observed. This shifts are upfield and consistent with the increasing of electron density in the carboxylate part upon deprotonation.

Several months later was reported about the preparation technique of imidazolium tartrate and its application as reagents for buffering pH in non-aqueous media[88]. The synthesis includes the preparation of an aqueous solution of imidazolium hydroxide [bmim]OH, which was prepared by passing the corresponding halide [bmim]Cl through a column of anion exchange resin. Obtained aqueous [bmim]OH was then neutralized with equimolar quantity of, adjusting the pH of the solution to the desired value by adding the aqueous solution of the tartaric acid. The solution was evaporated at 50°C and dried in vacuum at 50°C for 18 h to give a viscous ionic liquid **[bmim]-[(R,R)-Trtr]** (Figure 3-33).

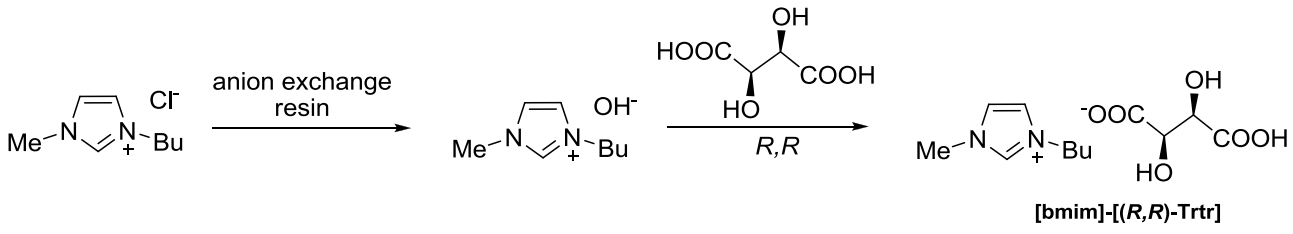


Figure 3-33. Synthesis of imidazolium tartrates ILs.

In 2008, was reported about the application of bis(imidazolium) tartrate **[bmim]2-[(R,R)-Trtr]** in the asymmetric hydrogenation of methyl acetoacetate[89], but no improvement in optical

yields were observed comparing to the Raney nickel asymmetric catalyst. Another compound **[omim]-[(R,R)-Trtr]** from this family was used as solvent for dissolving of water insoluble polyoxometalate coordination polymer[90]. Finally, the last known example for today of imidazolium tartrates is **[emim]$_2$-[(*S,S*)-Trtr]**, which was described by Amano *et al* in the patent as one of the components of resin composition[91] (Figure 3-34).

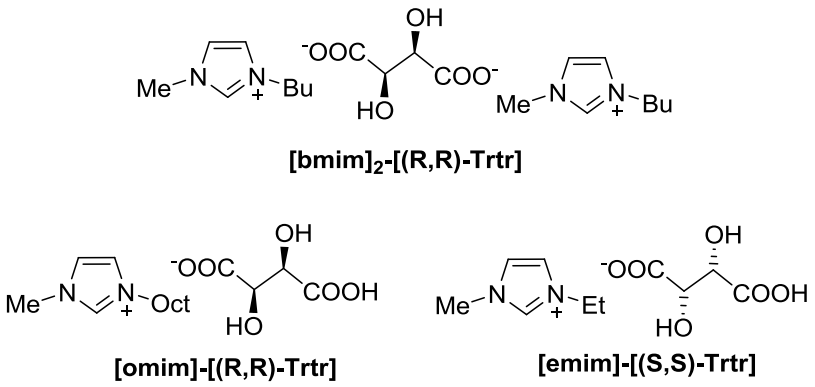


Figure 3-34. Known imidazolium tartrates.

During the preparation of this work, one article was published by Petrich and coll., where bis(tetrabutylphosphonium) (TBP) salts of (*R,R*)- and (*S,S*)-tartaric acid were prepared for the first time and used for inducing a stereoselective fluorescence quenching by photoinduced intramolecular electron transfer[92]. These tartaric acid-based CILs were prepared by reacting 2 equivalents of tetrabutylphosphonium hydroxide (40% commercial water solution) with 1 equivalent of (*R,R*)- or (*S,S*)-tartaric acid in cold methanol (Figure 3-35). Organic solvent was evaporated in a rotary-evaporator at room temperature to obtain a dense liquid, which was dried in vacuum oven (-30 in. Hg) at room temperature for 3 days. The authors of this work mention the importance of the absence of heating during the all parts of this synthesis. Otherwise, obtained IL will be colored in yellow, what can signify the formation of the impurities.

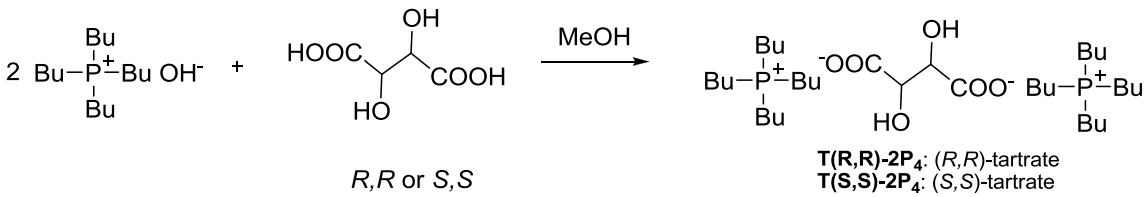


Figure 3-35. Synthesis of CILs from tartaric acid and tetrabutylphosphonium hydroxide.

Necessary to note that these tartaric acid-based CILs were prepared starting from the commercial source of tetrabutylphosphonium hydroxide without any verification of its concentration and the content of halogens. Low quality of the commercially available starting

material was the source of errors during the investigation of physical properties of the tartaric acid-based CILs by our team. The solution to resolve this problem is discussed in the part 4.2.6.

Tartaric acid forms solid salts with amino acid (*R*)-proline. Single crystal of (*R*)-prolinium-(*R,R*)-tartrate was grown up to 14 mm in length, and was shown to be a potential nonlinear optical material and promising dielectric material[93].

The examples of CILs syntheses based on chemical modification of tartaric acid carboxylic and/or hydroxyl functions are considered to be beyond of the scope of this chapter.

3.7 Proline and pipecolinic acid based ILs

First example of the synthesis of amino acid-based ionic liquid (AAIL) was published in 2005 by Fukumoto *at al*[59]. The series of 20 room temperature ionic liquids were prepared from 20 natural amino acids. Because amino acids coordinate transition metal ions, pure amino acid ILs cannot be obtained using the conventional method with metal salts. To limit the contamination of resulted ILs by halide salts and to limit the use of expensive metal salts was used the method that involves preparing imidazolium hydroxide to neutralize amino acids (Figure 3-36). Obtained **[emim]-[(*S*)-Pro]** has its glass transition temperature at -48°C, and represent a good example of chiral RTIL derived from natural resource.

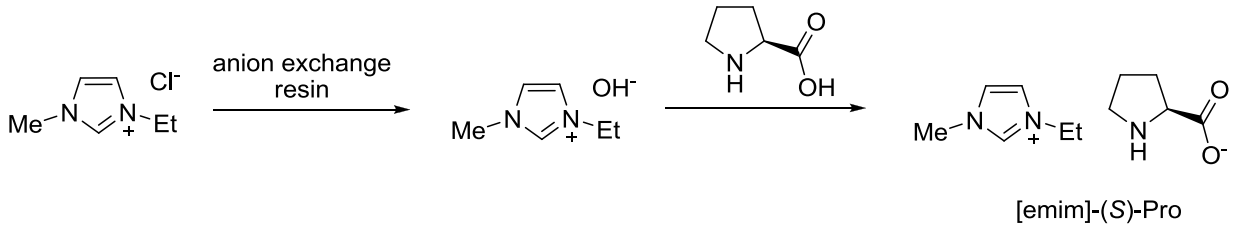
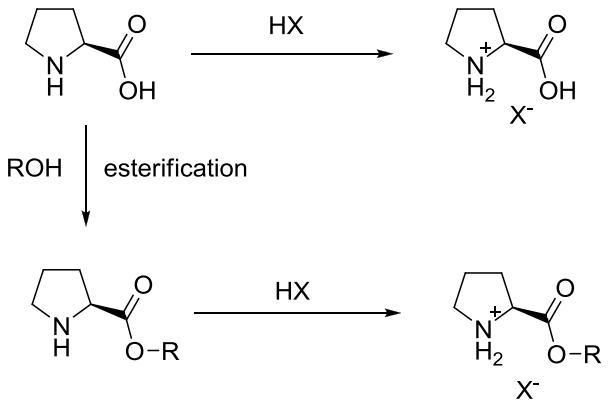


Figure 3-36. Synthesis of [emim]-(S)-Pro.

Several months later, Kou and coworkers have reported about two simple ways for ionic liquids preparation, in which the chiral cations are directly derived from natural α-amino acids and their ester salts were described[94]. Important to note that physical properties of the final ILs can be changed dramatically by simple esterification of starting amino acid, providing a great opportunity to prepare novel chiral ILs starting from naturally available resource (

Figure 3-37).



R	X	T_m or T_G, °C	R	X	T_m or T_G, °C
H	NO_3	Decomp.	Me	NO_3	-16 (T_m)
H	BF_4	76 (T_m)	Me	BF_4	-20 (T_G)
H	PF_6	Decomp.	Me	PF_6	-22 (T_G)
H	SO_4	92 (T_m)	Me	Lactate	-20 (T_G)
H	CF_3COO	78 (T_m)	Et	NO_3	-17 (T_m)

Figure 3-37. Preparation of different salts of proline.

Starting from (*S*)-proline, after esterification in the presence of $SOCl_2$ and subsequent anion exchange with $LiNTf_2$ in 2007 was prepared[95] ionic liquid **[HProOMe]NTf_2** (Figure 3-38). It was used as chiral solvent in the enantioselective homogeneous rhodium-catalyzed hydrogenation using tropoisomeric biphenylphosphine ligands to ensure the recycling of the catalytic system after extraction with *sc*CO_2.

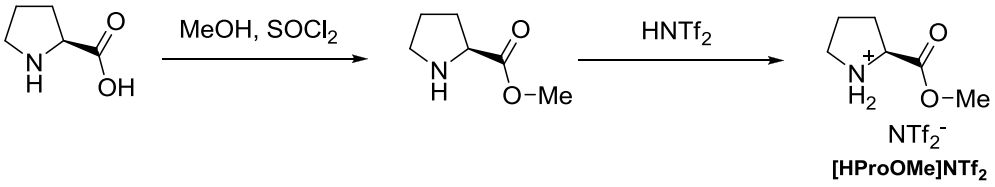


Figure 3-38. Synthesis of [HProOMe]NTf_2.

3.8 Phosphonium-Based Ionic Liquids

Phosphonium cation, the analogue of the ammonium cation, is a positively charged polyatomic ion with the chemical formula PR_4^+, resulting from alkylation of phosphine. Variation of the

four substituents on the phosphonium cation, and combining them with the numerous available anions, represents an enormous number of possible salts. More than 4000 different salts are reported up to 2011 and about 50 of them are commercially available. Recent review on the phosphonium cation-based ionic liquids unravels the impressive growth of interest for this class of compounds[96].

Investigated applications include use of phosphonium ILs as extraction solvents, chemical synthesis solvents, electrolytes in batteries and super-capacitors, and in corrosion protection. Phosphoniums are already manufactured on a multi-ton scale, and this is the good reason to consider them in an industrial process.

During our work we were interested particularly in one of the most common cations: tetrabutylphosphonium (commonly used abbreviations are $[PBu_4]^+$ or $[TBP]^+$ or $[P_{4444}]^+$ or $[PC_4C_4C_4C_4]^+$). Almost 1000 different salts are reported for the date.

Preparation of tetrabutylphosphonium proline **[PBu_4]-[(*S*)-Pro]** was first covered by patent[97] in 2005, and the next year published by Ohno *and coll*. in the study, showing lower viscosities and higher decomposition temperatures of tetraalkylphosphonium-based amino acid ionic liquids than their homologues ammonium-based amino acid ILs[98]. Tetrabuthylphosphonium proline salt was prepared by mixing proline with [PBu_4][OH] in aqueous solution (Figure 3-39). Resulted **[PBu_4]-[(*S*)-Pro]** has the low melting point at 25°C and good thermal stability up to 300°C.

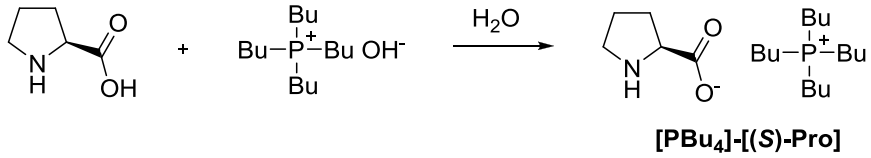


Figure 3-39. Synthesis of tetrabutylphosphonium proline.

The synthesis of tetrabutylphosphonium bis(trifluoromethylsulfonyl)imide **[PBu_4]NTf_2** was reported in 2005[99]. It has relatively high glass transition at 65°C due to its much smaller size and higher symmetry. It was prepared by the metathesis reaction between [PBu_4]Cl and $LiNTf_2$ in ethanol (Figure 3-40).

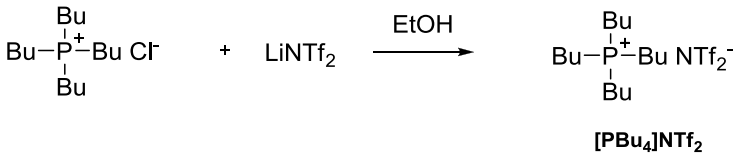


Figure 3-40. Preparation of [PBu_4]NTf_2.

Phosphonium tartrates are described in section 4.2.6 along with other tartaric-based compounds.

3.9 ELLE: Enantioselective liquid–liquid extraction

Enantioselective liquid–liquid extraction (ELLE) combines the principles of enantiomeric recognition and solvent extraction in one single technique. Enantiomeric recognition is crucial for ELLE because of enantioselective complexation which is responsible for the separation. Without enantiomeric complexation, enantioselective separation is not possible. Chiral complexes are formed as a result of interactions between the extractant with enantiomers and they are formed as a result of intermolecular interactions.

The use of liquid–liquid extraction for enantioseparation is known[6] since 1959, but development towards commercialization was suspended for many decades, till 2000s, mainly because of the lack of the suitable equipment. Very comprehensive and complete review was published in 2011 by the team of Feringa[2]. Underlying information of this chapter is referred to this work, unless other references are clearly stated otherwise.

Possible intermolecular interactions in enantiomeric recognition may consist of ion pairing, hydrogen bonding, π–π interactions, dipole-dipole and Van der Waals forces[100] (Table 3-2).

Type	Interactions	Energy, kJ/mole
Electrostatic (complementarity)	Ionic:	
	- with H bond	40
	- without H bond	20
	Ion-dipole	4-17
	H bonds	4-17
	Van der Waals forces	
	- Orientations forces (permanent dipole-permanent dipole)	4-17
	- Induction forces (permanent dipole-induced dipole)	2-4
Hydrophobic (similarity)	- Dispersion forces (induced dipole-instantaneous dipole)	4-17
	π-π interactions	4

Table 3-2. Noncovalent interaction forces: relative strength.

The complexation of a chiral host with a chiral guest can be schematically represented as the complementarity of two hands (Figure 3-41). The guest (blue hands) to shake the hand of the host (green hand) will offer its complementary right hand. This is the main idea of the three point attachment model, which states that more there are interaction points, more the complex will be stable (two are better than one and three are better than two).

Figure 3-41. Principle of enantiomeric recognition.

The field of molecular recognition was advanced in the 70's by Lehn and Cram giving the base to a wide spectrum of host–guest chemistry. Various approaches of discriminative interactions were reported, as recognition of neutral molecules, anions, carboxylic acids, amines, carbohydrates, peptides, proteins and the host–guest chemistry in general[101].

Another obligatory condition for the ELLE processes is the presence of two immiscible phases. Generally used system is water-organic solvent. At the beginning the substrate is dissolved in the aqueous phase. After that, the extractant is added, which is lipophilic and prefers the organic phase. The substrate interacts with the host and its transfer occurs. The upper example from the figure 1 is used to illustrate the interaction of the host with the substrate (Figure 3-42). One enantiomer has strongest interactions than other enantiomer. Finally, one phase will be enriched with one enantiomer and the aqueous phase enriched with the second enantiomer.

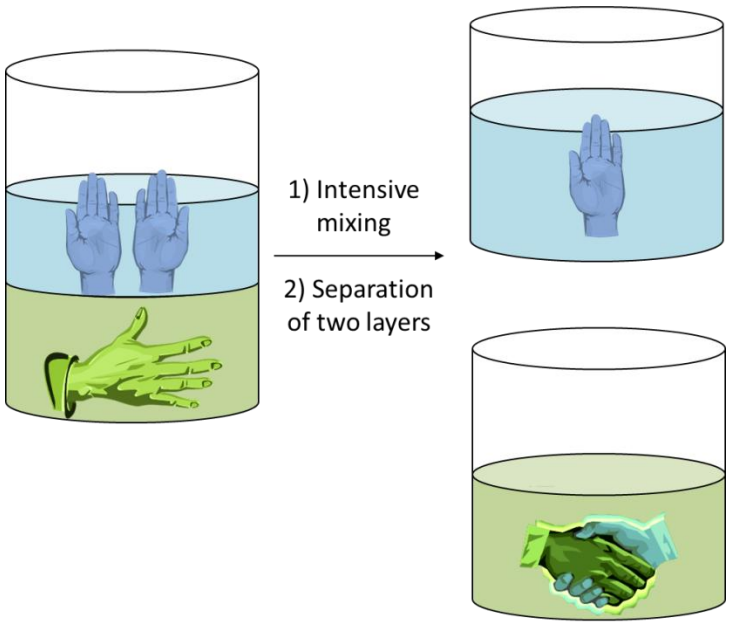


Figure 3-42. Principle of ELLE. Blue hands – racemic compound, green hand – host.

They were proposed two mechanisms of extraction. The first one is the homogeneous ligand addition mechanism, which comprises a homogeneous complexation in one of the liquid phases between host and guest. The second one is the interfacial ligand exchange mechanism which means the exchange of one of the ligands of host to extracted substrate. The two mechanisms are represented schematically on the Figure 3-43.

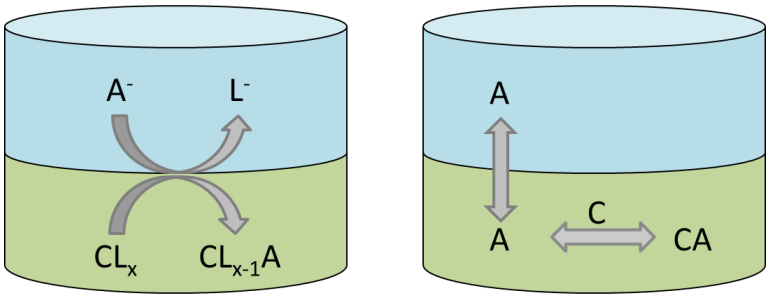


Figure 3-43. Two mechanisms of ELLE: homogeneous ligand addition mechanism and ligand exchange mechanism. A- substrate; C- host; L- ligand.

It is important to understand the complexation mechanism to effective process optimization. For example, the substrates as α-amino acids can exist in a neutral form and in a protonated/ deprotonated form, depending on the pH of media. That means that AAs can participate in both mechanisms of ELLE. During the extraction with interfacial anion exchange mechanism, the highest distributions will be found at a pH where AA prevails in the charged form. But when the homogeneous ligand addition mechanism is on the way, the highest distributions will be found at a pH where the neutral form of the AA dominates.

To describe the performance of ELLE process, single stage equilibria model is used. The simplest way to understand the efficiency of ELLE is to use the enantiomeric excess. But this is not enough to describe the performance completely because the ee is not an intrinsic example of an operational definition (Equation 3-1).

$$\mathrm{ee} = \frac{\mathrm{R} - [\mathrm{S}]}{\mathrm{R} + [\mathrm{S}]} * 100; \text{ when R>S}$$

Equation 3-1. Enantiomeric excess determination.

Operational definitions describe experimental observations. Another using example of an operational definition is the operational selectivity. The operational selectivity is the ratio of the distributions of the enantiomers, when one of two enantiomers is preferentially extracted (in the given example it is (*R*), Equation 3-2).

$$\text{a) } D_i = \frac{[i]_{org.\ all\ forms}}{[i]_{aq.\ all\ forms}};\ i = R, S; \qquad \text{b) } \alpha_{\mathrm{op}} = \frac{D_R}{D_S}$$

Equation 3-2. a) distributions (D_i); b) operational selectivity (α_{op}).

To both phases concentrations of all enantiomers are taken in account. For example, if in organic layer they are free substrate and in the form of complex with host, the sum of all molecules is calculated.

The operational definitions are not giving information on the intrinsic enantioselectivity of the extractant. To define the intrinsic selectivity of an ELLE system, the ratio of the equilibrium constants are used, which describes the preference in the complexation of the host with one of the enantiomers (in the given example it is (*R*), Equation 3-3).

$$\alpha_{\mathrm{int}} = \frac{K_R}{K_S}$$

Equation 3-3. The intrinsic selectivity of an ELLE system.

The complexation equilibria K_i depends on the mechanism of extraction (Figure 3-43) and may be defined for both extraction pathways. The constant K_i physically represents the sum of enantioselective and non-enantioselective interactions. When enantioselective interactions become more important that non-enantioselective, it becomes reflected in increasing of enantiomeric discrimination. Therefore, a single stage can be defined completely using the dissociation/protonation phase relations, the partition coefficient and the complexation equilibrium relations.

The main advantage of ELLE that there is no need to achieve a complete separation of enantiomers in a single stage. The satisfactory separation process can be developed using the technology in the multistage countercurrent process approach. With this multistage approach highly enantiopure compounds can be obtained in high yields using selectors that display only moderate selectivity. With this approach, it is not necessary to have the extreme selectivity of a single stage, as, for example, in asymmetric catalysis.

In continuous fractional distillation to calculate the minimum number of theoretical plates required for the separation of a binary feed stream by a fractionation column the Fenske equation is used. It can be applied for ELLE to determine the minimal number of required fractional extraction steps (N_{min}) for full separation of both enantiomers of the substrate with the desired ee of and operational selectivity (α_{op}) of a single extraction (Equation 3-4).

$$N_{\min} = \frac{\ln \frac{x_R\ (1 - x_R)}{x_S\ (1 - x_S)}}{\ln \alpha_{op}}$$

Equation 3-4. Minimal number of required fractional extraction steps. Fraction equivalents defined by x_R *and* x_S.

Separation becomes possible at moderate levels of α_{op} if using a fractional extraction CCS cascade with a reasonable number of fractional steps. The relationship trend between N_{min} and α_{op} is presented in Figure 3-44. As we can see, when α_{op} = 1.5, N_{min} is still 25. But it drops exponentially as α_{op} increases. Increasing α_{op} further than 7 affords only a slight decrease in N_{min}. This proofs the technology strength, because it is possible to separate a racemate with a limited number of stages. Normally it considered when the separation is imperfect that a fractional extraction scheme is needed. A minimal selectivity of 1.5 is generally viewed being necessary to avoid the requirement for an excessive number of fractional extraction steps[102].

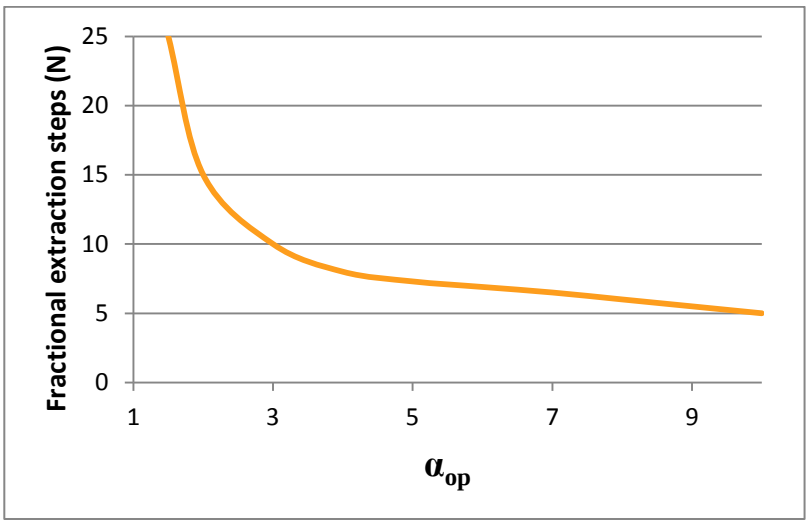


Figure 3-44. The relationship between fractional extraction steps and α_{op}.

The relationship between the desired ee and N_{min} is dependent on α_{op}. If, for example, α_{op} will be equal 7.0, only 4 stages will be required to obtain 95% ee, and only 7 stages to obtain an ee as high as 99.8% ee (Figure 3-45).

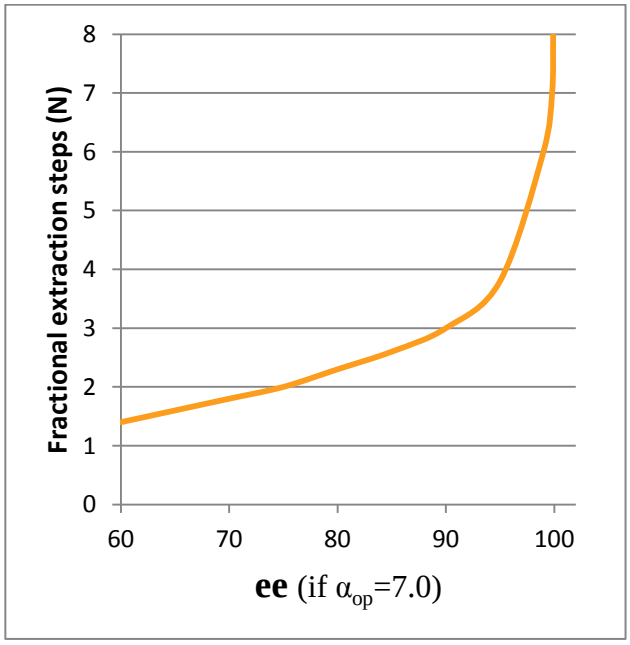


Figure 3-45. The relationship between operational selectivity (α_{op}) and ee.

The smallest number of stages to resolve a specific compound, the larger the process ability for that compound. This opens the way to optimization possibilities in a multi-product environment: various combinations of process conditions can result in the desired product specifications. All systems for which a single stage selectivity of 1.5 was obtained can be separated in a multi-product extractor containing 50 stages[103].

Another condition, necessary to achieve good separation is the quantity of the host. The minimal excess of extractant around 1.5 is needed. If there is no excess of extractant over the enantiomers, a full separation can never be obtained. Without excess, the extractant will eventually become fully loaded, and adding more stages will not increase the product purity any further. Therefore, the extractant always has to be present in some excess. Suitable quantity should be studied for each compound separately[103].

They are several configurations of the multistage fractional extraction, such as cross-current multistage extraction, counter-current multistage extraction and fractional extraction[103] (Figure 3-46).

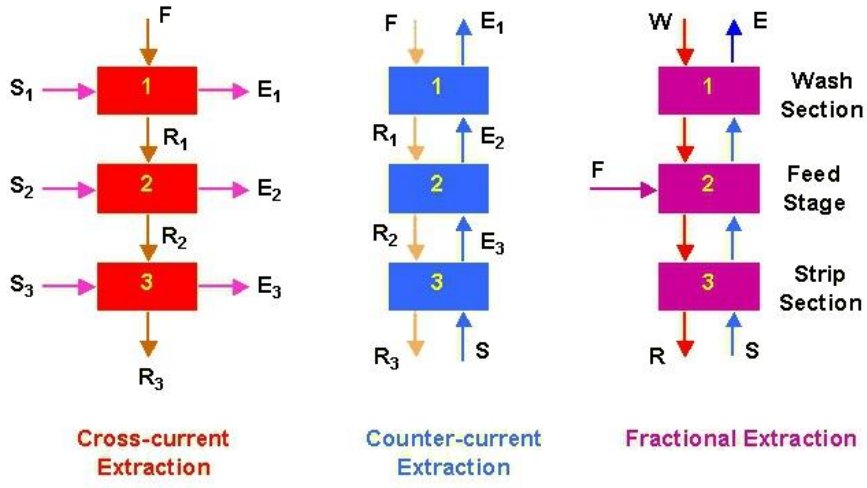


Figure 3-46. Three possible types of the multistage extraction. W- wash; F- feed; S- solvent, R- raffinate.

Cross-current extraction is a good laboratory process because each stage is made up of an equilibrium stage where the 2 liquid phases are mixed together for a period of time until equilibrium is reached. Each phase is then allowed to coalesce and is separated by decanting. Fresh solvent is added to each stage. This technique is rarely used in a commercial process because of the large volume of solvent required and the low concentration of solute in the extract.

Counter-current extraction is widely used in industrial processes. The solvent S enters the stage on one end, opposite to the feed F at the other end. The two phases flow counter-current to each other. The objective is to strip one or more components from the feed liquid. In contactors with actual stage devices, the phases will be separated before leaving each stage. If the contactors are differential devices, one of the phases can remain as the dispersed phase

throughout the contactor, before being allowed to coalesce at the end of the device prior to being discharged.

Fractional extraction usually involves 4 components, in order to separate at least 2 components from a feed mixture. Two immiscible liquids travel counter-currently through the contactor. The primary solvent S preferentially extracts (strips) one of the components from the feed, while a wash solvent preferentially scrubs the extract the unwanted solute. In this manner, the 2 components in the feed can be separated quite like the rectification in continuous distillation of binary mixture. Fractional extraction is considered as the most efficient configuration to apply in ELLE process.

Enantioselective liquid–liquid extraction equipment used in the chemical industry is widely developed. All kinds of used extractors can be classified in two basic types: the mixer–settlers which consist of discrete stages and are used for all separation processes, and the extraction columns that are mostly applied in extraction processes. Selection of the most suitable type is dependent on the process conditions and constraints.

Commonly for laboratory use, U-tubes are preferred and their modifications, because of possibility to determine exactly interfacial areas and mass transfer characteristics. Also, some examples of membrane technology are known. Very high purities may be obtained with limited amounts of precious hosts using this technology; however its practical use is limited. Long time the use of ELLE was limited only to a demonstration and the proof of principle using the techniques discussed above. It was due to the large volumes of solvents and hosts required in the traditional types of continuous extraction equipment. Until recently it was not reported about the design of the continuous ELLE processes using only moderate selectivity extractants. But after designing of centrifugal contactor separators (CCS) the situation changed. CCSs use only small amounts of the precious chiral extractants for multistage continuous process.

Centrifuge force speed up liquid-liquid separations by improving the specific gravity difference between the two liquids. Two immiscible liquids with slight density differences can be separated rapidly and cleanly and on a continuous basis by a centrifuge. Liquid-liquid dispersions that require hours to separate at 1”G” can be greatly improved both in speed and efficiency at 200 “G”. With this speed, it was demonstrated that one experimental stage corresponded with an equilibrium stage.

Mixed liquids (green, Figure 3-47) of any ratio and with differing densities are continually pumped or injected by the gravity into one of the inlets. The liquids are quickly separated by

the large centrifugal forces. The heavy phase (blue) will move toward the rotor wall and the light phase (yellow) will settle on top of the heavy phase. In the top of CCS the separated phases are able to exit the rotor for discharge. Great advantage of CCS is that through the use of centrifugal force only small amounts of liquids are needed and they can be set in series to apply the fractional extraction scheme (Figure 3-47).

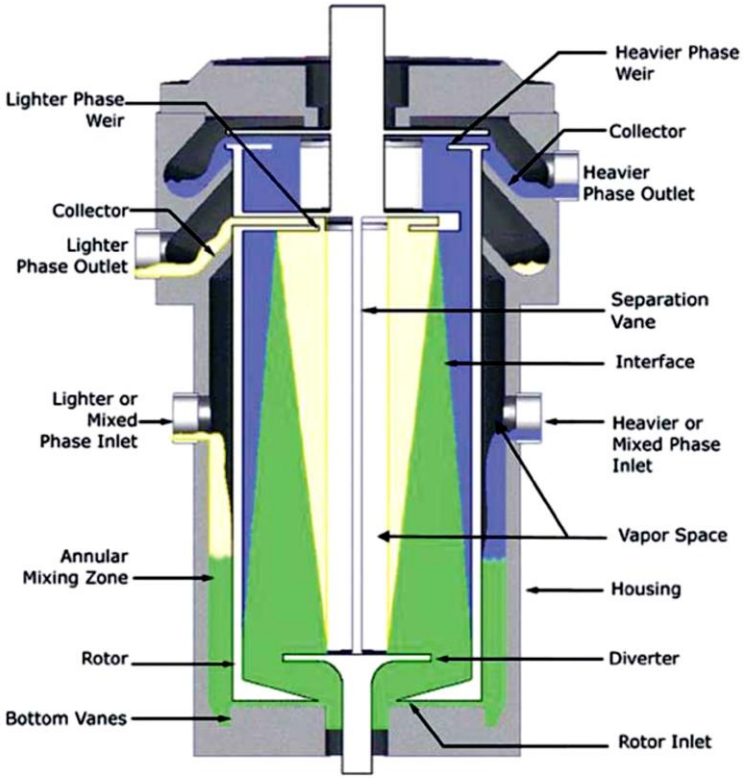


Figure 3-47. Centrifugal contactor separator from CINC Solutions ©, Doetinchem, The Netherlands[104].

First who demonstrated that ELLE is possible in continuous centrifugal contactor separator equipment were Heeres *et al* [105]. It was demonstrated for a model system composed of a racemic mixture of protected amino acid DNB-(*R,S*)-Leu with a host of chiral cinchona alkaloid (Figure 3-48). Optimum conditions were found to give the ee 34% and the L-enantiomer yield 61%. It was shown also that the back extraction of the host is almost quantitative at pH>9. Considering the operational limits of the laboratory size CCS equipment, the separation capacity of 10 kg of racemate/week was predicted to be possible.

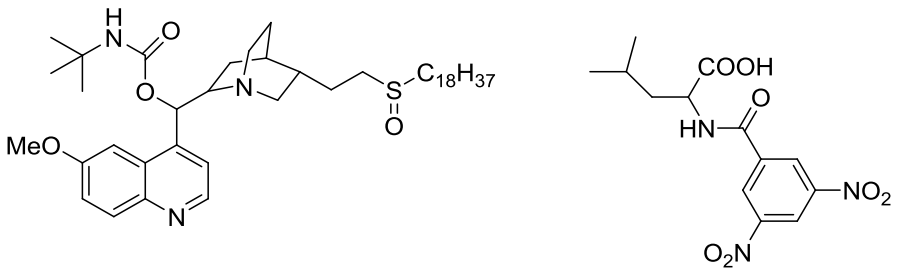


Figure 3-48. Host of chiral cinchona alkaloid and resolved protected leucine.

Successful examples of amino acid extractions are not limited to the previous one. In 2008, it was reported about the successful extraction of one enantiomer into an organic phase by selective coordination to a hydrophobic selector, to leave the uncomplexed enantiomer in an aqueous phase[86]. Resolution of racemic *N*-benzyl α-amino acids (*N*-Bn-AA) has been achieved by a liquid-liquid extraction process using the lipophilic chiral cobalt(III) complex derived from DACH. As a result of the resolution by extraction, one enantiomer (*S*) of the *N*-benzyl α-amino acid predominated in the aqueous phase, while the other enantiomer (*R*) was driven into the organic phase by complexation with cobalt. The complexed amino acid (*R*) was then quantitatively released by a reductive Co(III)-Co(II) counter-extraction with aqueous sodium dithionite or L-ascorbic acid in methanol. Treating the Co(II) complex with 2 equivalents of racemic (*N*-Bn)-Ala, followed by extraction with $CHCl_3/H_2O$, led to enantiomeric excesses of 94% (*R*) for the complexed [Co(III)(*N*-Bn)-Ala] and the and 93% of uncomplexed amino acid (*S*) respectively (Figure 3-49). The major drawback of this approach resided in the necessity to use rather hard conditions like the reduction with $NaBH_4$ to release the complexed amino acid. This example is particularly interesting because of use DACH, which was one of research subjects of our work.

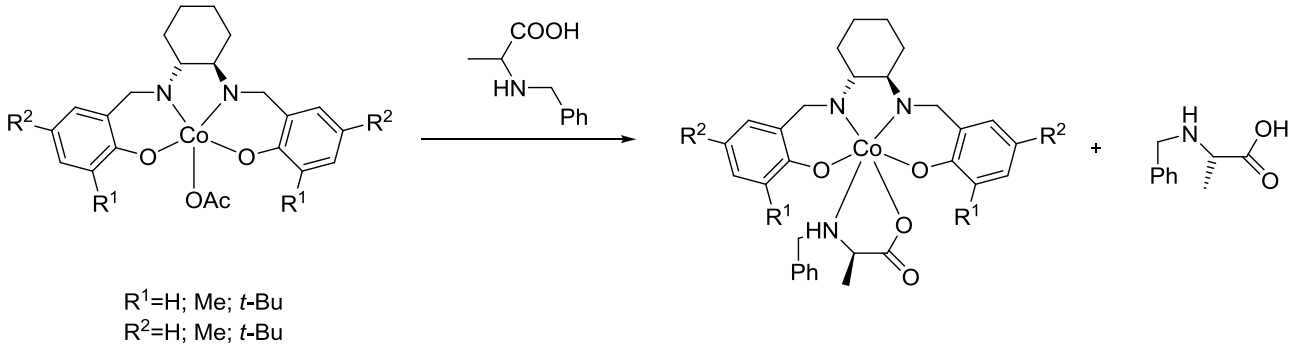


Figure 3-49. Chiral cobalt host and resolved alanine derivative.

Amino acids are the major substrate studied in ELLE because of their importance to chemical and biological applications. Overview of hosts[2], used in ELLEs of amino acids and their

derivatives, along with the number of examples tested and the results are listed in the Table 3-3.

Substrate	Host	α_{op}	ee	Number of examples
α-amino acid and α-amino acid ester salts	Cram dilocular host	1-31		23
α-amino acids and ester salts	BINOL-crown ether	1.1–19.5		6
α-amino acids	Guanidium-crown ether		up to 30%	1
α-amino acids	Proline derivative Cu(II) complexes	1.0–4.5		5
α-amino acids	Lanthanide(III) tris(b-diketonate) complexes	up to 2.2		6
N-Cbz α-amino acids	Metalloporphyrins		up to 96%	15
α-amino acids	Palladium–BINAP complexes	1.1–7.0		22
N-Acyl α- and β-amino acids	Salen–cobalt(III) complexes		90–96%	7
Amino acids	D2EHPA and tartaric acid derivative	1.36–5.3		4
N-Protected α-amino acids	Carbamoylated quinine Derivatives	3–5		
N-Acyl amino acids	Steroidal guanidinium		up to 10 : 1	8
DNB-*N*-protected α-amino acids	Deoxyguanosine derivatives	1.15–3.03		6

Table 3-3. Successful examples[2] of amino acids enantioselective extractions.

For many years, good operational selectivities were only achieved with chiral hosts constructed from crown ethers and similar structures. In 2006, it has been shown that reactive extraction does not need to be limited by crown ether systems to reach good operational selectivities. Afterwards, it was proven experimentally that complete separation of a racemate can be achieved using only the hosts with intermediate selectivity. It was possible after the development of multistage countercurrent cascade separators.

Another field to improve ELLE's productivity was shown. The host can be present in both phases of ELLE. In 2009, it was reported about the new chiral separation method: biphasic recognition chiral extraction for the separation of mandelic acid enantiomers[106]. Distribution behavior of mandelic acid enantiomers was studied in the extraction system with tartaric acid derivative (D-(1)-DTTA) in organic phase and β-CD derivatives in aqueous phase, and the influence of the types and concentrations of extractants and pH on extraction efficiency was

investigated (Figure 3-50). D-(1)-DTTA preferentially recognizes *R*-mandelic acid. Hydroxypropyl-β-cyclodextrin (HP-β-CD), hydroxyethyl-b-cyclodextrin (HE-β-CD), and methyl-β-cyclodextrin (Me-β-CD) have stronger recognition abilities for (*S*)-mandelic acid than those for (*R*)-mandelic acid, among which HP-β-CD has the strongest ability. Both pH and the concentrations of extractants have great effects on chiral separation ability. High enantioseparation efficiency with a maximum enantioselectivity of 1.527 is obtained at pH of 2.7 and the ratio of 2:1 of D-(1)-DTTA to HP-β-CD. The obtained results indicate that the biphasic recognition chiral extraction (when chiral hosts are present in both phases) shows strongest chiral separation ability than the monophasic recognition chiral extraction (when chiral host is present only in one phase).

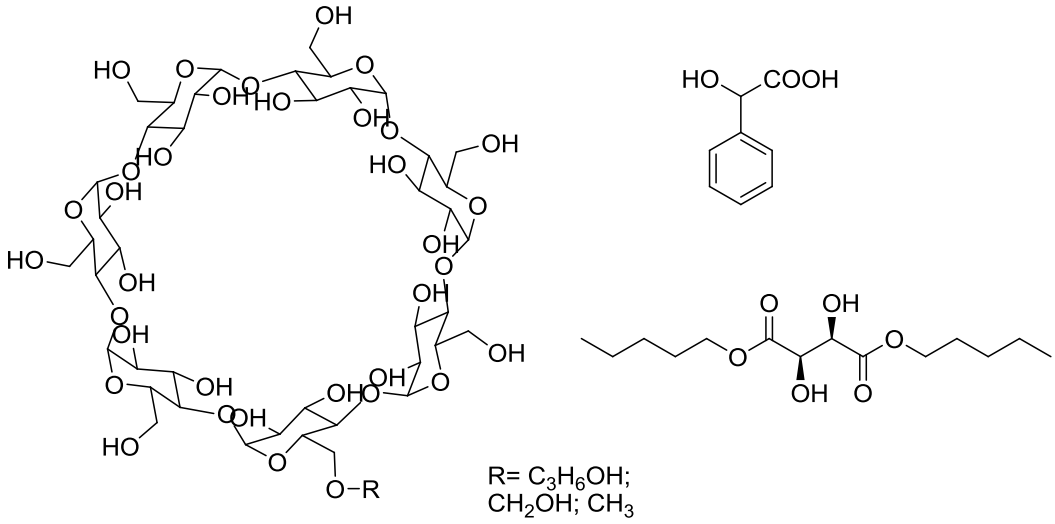


Figure 3-50. Biphasic recognition system comprised β-cyclodextrin derivative, L-dipentyl tartrate and mandelic acid.

The discovery of flexible extractants for racemate separations will short the time for new routes of preparation of chiral compounds. It will be better if a single extractant could be applied to separate a wider range of racemates. That is why the search for new synthetically accessible versatile extractants with a high selectivity towards a wide substrate scope is the main condition to reduce the development time for the separation processes.

Chiral ionic liquids can be possibly the best candidates to be applied in ELLE, because they can play the role of chiral selector and the solvent simultaneously. In addition, they can be derived from renewable chiral pool, be non-toxic, biodegradable and correspond to other principles of green chemistry.

Environmentally safe ionic liquids for chiral resolution were appearing in 2004 in Japan patent[107]. Isoquinolinium-based IL was treated with (*D,L*)-Tyrosine to remove 18% of L-Tyr from the aqueous phase (Figure 3-51). Despite this early example, no continuation was published.

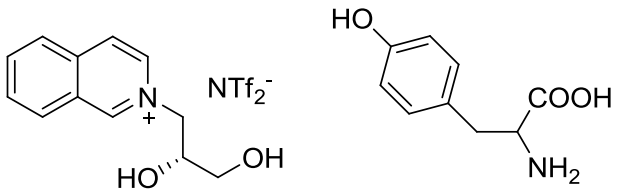


Figure 3-51. Extraction of (R,S)-Tyrosine from isoquinolinium-based IL.

Next and the last for the moment example of ELLE using CILs was published only 6 years later by a Chinese team[108]. The ee values varied from near 0 up to 50% for single-step extraction. Ligand-exchange mechanism between the copper complex of CILs was responsible for enantioselective enrichment of racemic amino acids. This complex was prepared by reaction of alkylimidazolium cation and prolinate anion (Figure 3-52). In this example of ELLE, the CIL was the host and the organic solvent in the same time. The efficiency and the enantioselectivity of the extraction system were reported to be dependent on different factors as CIL structure, copper ion concentration, organic phase and amino acid concentration.

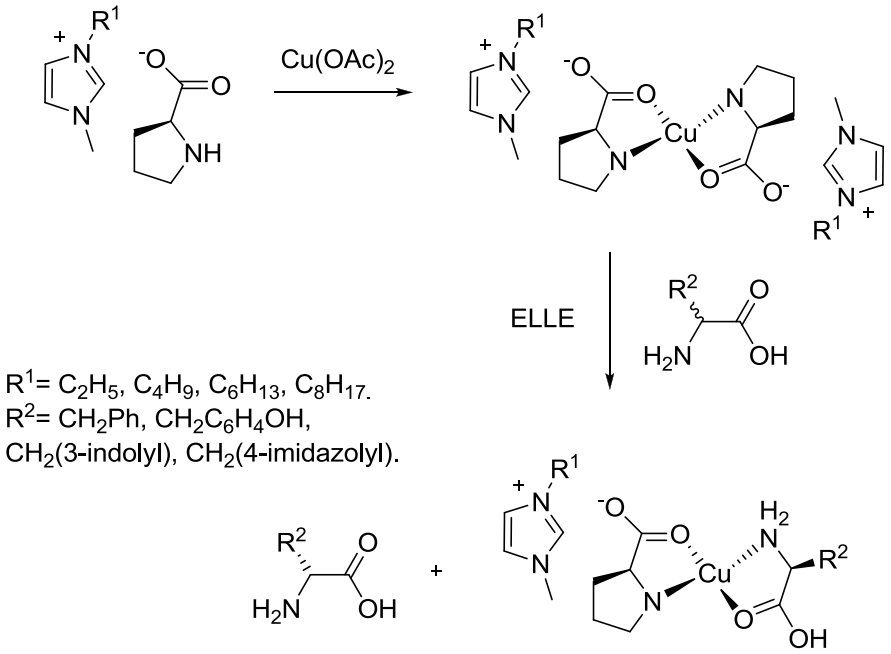


Figure 3-52. ELLE using CILs passing through ligand-exchange mechanism.

The last two examples are proving that the direction, chosen by our team in the beginning of this work is correct, and can led to new efficient approaches in the field of liquid phase

resolution methods. They will help to bypass the problem of handling large amounts of solid materials in industry, resulting in reducing the cost, time and environmental impact of the purifications processes.

4 Discussion of results

All applications of CILs in asymmetric synthesis, spectroscopic and chromatographic techniques, described in the bibliographic part, confirm the chiral recognition property of CILs. It makes possible to discriminate one enantiomer from the other using CILs. This encourages to continue the search for new, more efficient, more simple and cheaper applications of CILs in the preparation of enantiomerically pure compounds.

Our idea was to develop the enantioselective liquid-liquid extraction (ELLE) of enantiomers by chiral ionic liquids, using them simultaneously as a solvent and chiral selector. The attraction of this method is that it may avoid the use of excessive handling of solids, which is often the slowest step in the process of resolution of diastereomeric salts by crystallization during the production in ton scale.

No information was available about ELLE in ILs in the beginning of this work. This idea stayed unexplored until 2010 (excepting one Japanese patent published in 2004), when the first successful approach in this field was reported[108] (for complete bibliographic research in this field see part 3.9). So it was necessary for us to develop a complete pathway for ELLE with CILs starting from zero. Proposed way consisted of the next steps:

- Choice of racemic substrates
- Preparation of hosts - CILs
- Choice of co-solvent ILs
- Choice of second solvent for biphasic system
- Solubility tests of chosen substrates
- Screening of all substrates with all hosts
- Cross-metathesis
- Modification of substrates to use in cross-metathesis
- Screening of modified substrates with tetrabutylphosphonium tartrates
- Study of important parameters for one chosen system

Every step is interconnected with the next one. For example, the chemical structure of a racemic substrate will determine the motive of structure of the chiral host, which must have

chemical functions complementary to the chosen substrate, in order to ensure strong interactions. Chosen host must prefer to stay only in one of two phases, when chosen substrate must be soluble in both, etc.

Every step is described in details below.

4.1 Choice of racemic substrates

To choose the racemic compounds to be resolved, the next principles were used. The structure of these compounds needs to contain chemical functions commonly present in a large number of chemical substances to enlarge the number of possible resolvable structures and thus to facilitate the introduction of ELLE into industrial processes. Chosen compounds must be stable to ELLE conditions and not destroy any component of the system. By preference, they need to be racemisable to ensure their complete recovery if the process will be commercialized.

From the literature we know that the most studied classes of compounds in ELLE are amino acids. We decided also to work with amino acids because of their irreplaceable role in nature and in organic synthesis. One naturally occurring AA was chosen – proline **Pro** – along with its homologue pipecolinic acid **Pip** (Figure 4-1). Also, one derivative of both AAs was added: silaproline **Sip** and pipecoloxylidide **Pipeco**.

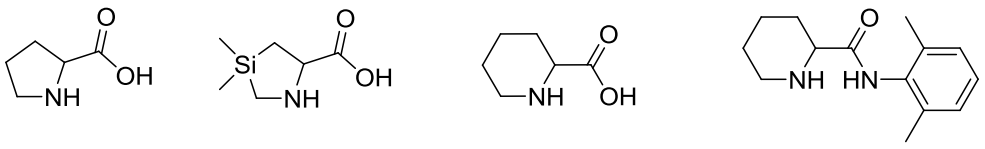


Figure 4-1. Four racemic substances chosen for ELLE in ILs.

Silaproline (γ-(dimethylsila)-proline) is the silicon-containing equivalent of proline and it is used as structural tool for biochemical investigations. It has the increased lipophilicity which facilitates membrane permeability and it has reduced sensitivity to enzymatic degradation[10].

Pipecoloxylidide was the model compound of the INTENANT project and was supplied in racemic form from AstraZeneca. It is an intermediate for the synthesis of the commercial drugs mepivacaine, ropivacaine and bupivacaine, which are local anesthetics. For the moment, useful

(*S*)-enantiomer is obtained through the diastereomeric salt resolution with *O,O*-dibenzoyl *L*-tartaric acid[109].

All chosen compounds possess an α-amino acid function or derived from it (pipecoloxylidide). This chemical similarity was taken into account during the preparation of chiral hosts.

4.2 Preparation of hosts - CILs

The major obstacle for the introduction of fractional reactive extraction as a chiral separation method in the chemical and pharmaceutical industries is the lack of versatile enantioselective extractants.

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Considering that there are just few examples of commercially available chiral ionic liquids, the first step of our research was the preparation of several families of chiral ionic liquids bearing at least one function able to interact with racemic mixtures. Of course, those ILs must be chiral. As our chosen racemic targets contain α-amino acid function, we decided to prepare CILs with at least one acid or/and base function. In this case it could be possible to ensure the interaction between substrate and host via ion paring, i.e. by the strongest possible noncovalent way (see Table 3-2).

We chose to prepare three different families of CILs: histidinium-, tartrates and cyclohexanediamine-based compounds (Figure 4-2). Also, one commercially available CIL, derived from phenylethylamine, was ordered from the Solvionic company.

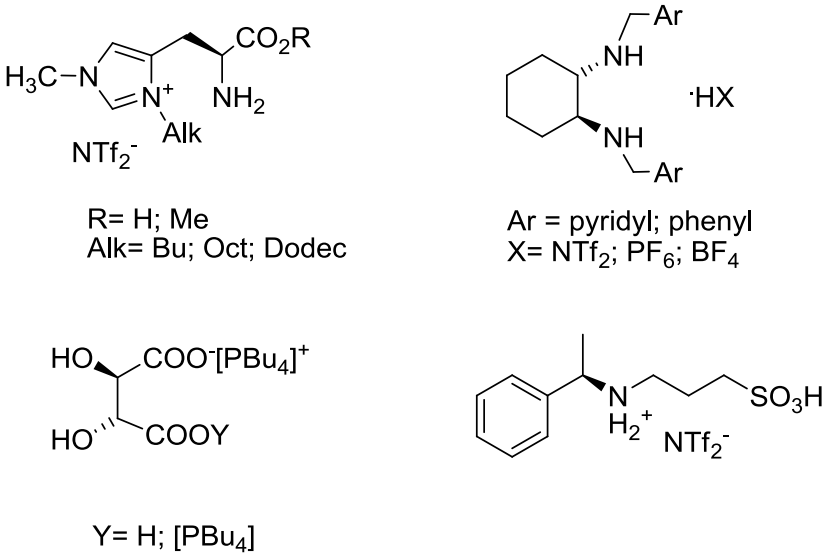


Figure 4-2. Chiral ionic liquids chosen for ELLE.

Besides the main criteria of CILs choice as the presence of acid or/and base functions another factors were considered to be essential for success. Those acid or/and base functions need to be connected with the center of chirality to increase the probability of enantiomeric interaction. They must be lipophilic (because chosen racemic substances are generally hydrophilic), to ensure their presence only in one of two phases. They must be simple in preparation and easily scalable to be accessible for commercialization. They need to be inert to ELLE conditions and do not destroy any component of the system. By the preference, they need to be derived from renewable source and to cover other criteria of the green chemistry. They need to be stable in time to ensure their reusability.

All (or almost all) of mentioned above criteria were reflected in the chosen CILs. Their preparation and properties are described in details below. In total, 14 CILs were selected for ELLEs: 5 histidiniums, 6 DACH-based compounds, 2 tartrates and 1 phenylethylamine.

4.2.1 Synthesis of new histidiniums

(S)-Histidine is shown to be a powerful chiral precursor for the construction of a new series of imidazolium-containing chiral ionic liquids, in which the chiral bifunctional unit of the amino acid remains unchanged. We envisioned (S)-histidine, a commercially available natural amino acid , as a key chiral starting material for the elaboration of dissymmetric imidazolium moieties by direct modification of the side chain, thus leaving free the amino acid function of the obtained chiral ionic liquids. Chiral amino acid part seems to be the best candidate for separation processes because of possible strong acid-base interactions. Indeed, the side chain of histidine has an imidazole ring from which some imidazolium ionic liquid type (most commonly used cation in ionic liquids) can be constructed. The chiral bifunctional unit of amino acid remains intact (Figure 4-3).

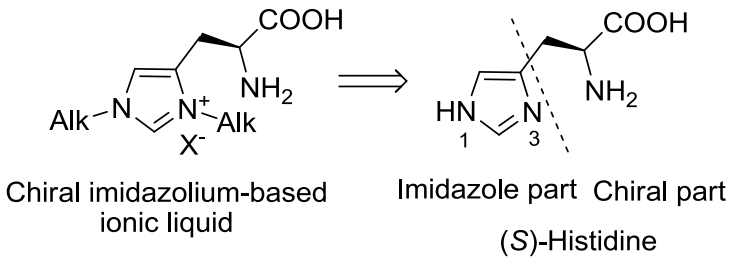


Figure 4-3. Retrosynthesis of histidinium-based ionic liquids.

Imidazolium cation part can be modified by varying the substituent on intracyclic nitrogen atoms (without touching the part of the amino acid salt). Desymmetrization of imidazolium cation lowers the melting point. The melting points of organic salts are closely related to the symmetry of ions, the higher is the asymmetry, the lower is the melting point. The symmetry allows efficient stacking of ions in the crystal. Conversely, the asymmetry of the cation creates a distortion of the crystal mesh, leading to a decrease in melting temperature.

Histidine has three nucleophilic nitrogen atoms with different reactivity. For regioselective alkylation of the nitrogen atoms of the imidazole ring, they must be treated independently. The nitrogen atom in position 1 is more reactive than the nitrogen atom in position 3, mostly for steric reasons. In literature, there are methods to alkylate selectively position 3 to position 1 [62].

The chosen strategy was developed previously in our team[62], and it allows to alkylate nitrogen atoms of the imidazole ring without affecting the nitrogen atom of the amino acid part.

First step is amine group protection in position 3 (Figure 4-4). Mixture of carbonyldiimidazole and salt of methyl ester of histidine with vigorous mechanical stirring gives a viscous liquid after 30 minutes at 80 °C. After hydrolysis and extraction with dichloromethane, cyclic urea **H01** was obtained with good yield and excellent chemical purity after simple washing with diethyl ether.

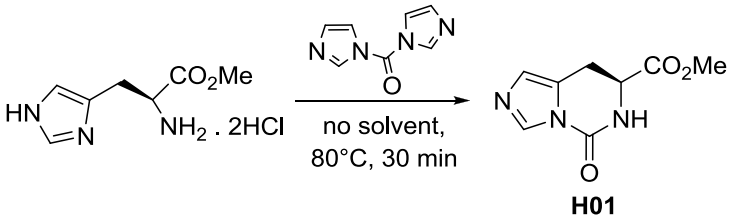


Figure 4-4. Amine group protection by carbonyldiimidazole.

Second step is the alkylation in position 1 of the cyclic urea **H01**. It was performed with methyl iodide to bring for our product resemblance to the ionic liquid of [bmim]-type. The alkylation with methyl iodide is carried out under mild conditions, with heating at 40 ° C for 16h. The resulting salt was slightly soluble in acetonitrile, and precipitated partially during the reaction. After evaporation of acetonitrile, the compound **H1** was taken up in acetone, a solvent in which it is totally insoluble. It was obtained as white crystals in quantitative yield (Figure 4-5).

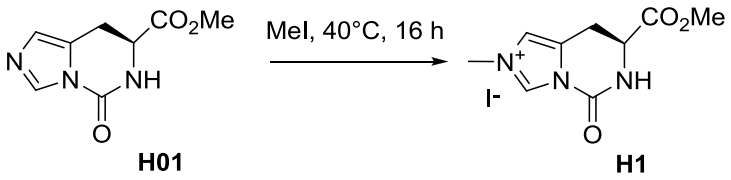


Figure 4-5. N-alkylation in position 1 of the cyclic urea.

The third step is opening of the cyclic urea **H1** by tert-butanol, which allows both to release the nitrogen atom in position 3 and to protect the amine of histidine. A solution of methylated compound **H1** in *t*-butanol was heated in the presence of one equivalent of diisopropylethylamine. Contrary to the previously published time of this reaction equal to 3 hours, it took 24 hours to obtain the methyl ester of N-Boc-1-methyl-L-histidine **H2** with a yield about 70% (Figure 4-6).

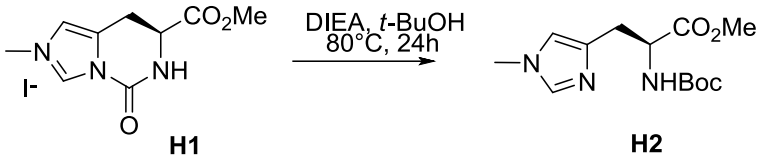
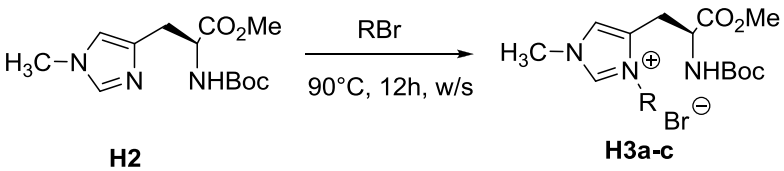


*Figure 4-6. Opening of the cyclic urea **H1** by tert-butanol.*

The next step in the described synthesis[64] was the alkylation of nitrogen in third position. The alkylation was performed with *n*-butane bromide to give the product **H3a** in 94% yield (Figure 4-7).

One of the goals of this work was the preparation of water insoluble chiral ionic liquids. To increase the hydrophobicity of final compounds, the imidazolium cycle of compound **H2** was alkylated by us with *n*-octyl bromide and *n*-dodecyl bromide at 90°C for 12 hours and without solvent, giving new salts, **H3b** and **H3c** with yields 98 and 95% respectively.



H3	R	Yield, %
a	*n*-Bu	94
b	*n*-Oct	98
c	*n*-Dodec	95

*Figure 4-7. N³-alkylation of compound **H2**.*

In the previous work, compound **H9a** was directly introduced to a metathesis step with the salts $LiNTf_2$, KPF_6 or $NaBF_4$. Afterwards, all NTf_2^- salts were introduced to deprotection reactions, common for amino acid chemistry (Figure 4-8).

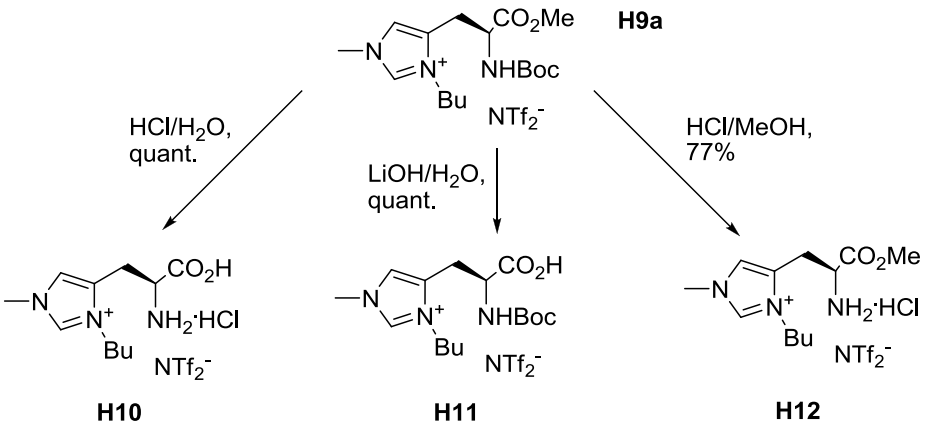
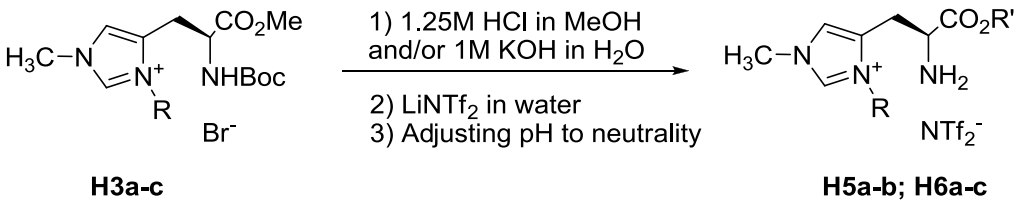


*Figure 4-8. Selective or complete deprotection of **H9a**.*

Compound **H10** was reported to be completely soluble in water when containing hydrophobic NTf_2^- moiety[64]. It can be explained by the formation of a hydrochloride residual from the deprotection step. But in this case, the exact position and stoichiometry of NTf_2^- anion remain uncertain. Compounds **H11** and **H12** were also described to be NTf_2^- salts after the deprotection conditions. But those conditions might change the molar ratio of NTf_2^- by ion metathesis with other anions, present in reaction media.

We developed another strategy in order to achieve the goal to dispose hydrophobic bifunctional ionic liquids. Ion metathesis was moved to be the last step of synthesis, preceded by deprotection of Boc protective group by acid treatment and/or saponification of methyl ester protective group (Figure 4-9).



Number	Code	R	R'	Yield, %
H5a	[mbHis-OMe]-[NTf_2]	*n*-Bu	Me	57
H6a	[mbHis]-[NTf_2]	*n*-Bu	H	58
H5b	[moHis-OMe]-[NTf_2]	*n*-Oct	Me	60
H6b	[moHis]-[NTf_2]	*n*-Oct	H	68
H6c	[mDodecHis]-[NTf_2]	*n*-Dodec	H	85

Figure 4-9. One-pot deprotection of amino acids and ion metathesis.

Deprotection step(s) with anion metathesis were carried out in one-pot in this research. The resulting ionic liquid precipitates from water solution when adjusting pH to 7, which might be near of the isoelectric point of the amino acid. All resulted ionic liquids can be dissolved in water solution of acid or base and re-precipitated when shifting pH near to 7. It can be explained by formation of salts of amino acid function by protonation/deprotonation under acid/base conditions. At neutral pH, close to isoelectric point, amino acid exists in free form (zwitterionic) decreasing its solubility.

Selective precipitation can be used as suitable purification method for hydrophobic ionic liquids containing amino acid part. This method was scaled up to multigram quantity and showed good results as a simple preparation way for hydrophobic ionic liquids containing amino acid part in the structure.

In order to determine the phase behavior of all obtained salts, DSC analyses were performed. All compounds **H3; H5-H6** have glass transition points below 0°C, confirming their ionic liquid nature (Table 3-1).

Number	Code	T_g, °C	$[\alpha]_D$, c=1 (MeOH)
H3a	[mbHis-Boc-OMe]-[Br]	-9.2	-15,8
H3b	[moHis-Boc-OMe]-[Br]	-23.5	-12.4
H3c	[mDodecHis-Boc-OMe]-[Br]	-37.3	-10.5
H5a	[mbHis-OMe]-[NTf_2]	-44.6	+4.3
H6a	[mbHis]-[NTf_2]	-16.6	+0.9
H5b	[moHis-OMe]-[NTf_2]	-18.7	+1.8
H6b	[moHis]-[NTf_2]	-29.6	+2.3
H6c	[mDodecHis]-[NTf_2]	-28.5	+0.9

*Table 4-1. DSC and $[\alpha]_D$ analyses of ionic liquids **H3**, **H5-H6**.*

Visible correlation structure-glass transition is present in the series of bromides **H3a-c**. The increase of alkyl chain length decreases the glass transition point. Longer alkyl chains create a distortion of the crystal mesh, leading to a decrease in melting temperature.

Optical rotation measurements confirm chirality conservation after all reaction steps (Table 4-1). Optical rotation of bromides **H3a-c** is counter-clockwise, when all other ionic liquids **H5-H6** turn polarized light clockwise.

4.2.2 Preparation of 1,2-diaminocyclohexane-based ionic liquids.

One of our goals in the frame of the INTENANT program was the synthesis of modified 1,2-diaminocyclohexanes. It was planned to obtain all possible homologues by reaction between (1*S*,2*S*)-diaminocyclohexane with benz-; pyridyl-2-; pyridyl-3- and pyridyl-4- aldehydes (Figure 4-10). At the beginning of this project in 2008 only two compounds **D2,2** and **D4,Ph** of this series were known. Compound **D4,Ph** only as *R,R*-enantiomer. In 2009 was reported about the synthesis of two *R,R*-enantiomers of compounds **D4,4** and **D3,3**.

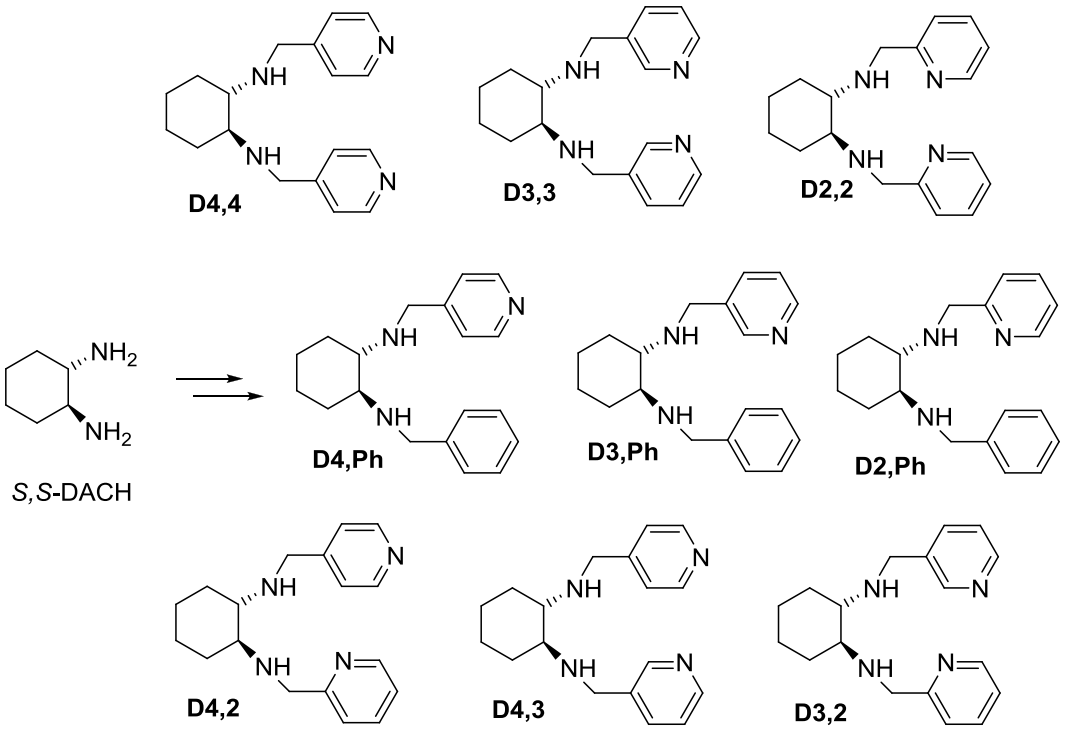


Figure 4-10. Prepared (1S,2S)-diaminocyclohexane-based compounds.

All compounds were planned to serve for two purposes: to provide them to the team of Gérard Coquerel (INTENANT WP4 "Crystallization") in Rouen University for tests of auto-seeded preferential crystallization and to create a new class of chiral ionic liquids.

Also, two racemic compounds were synthesized only for preferential crystallization applications (Figure 4-11).

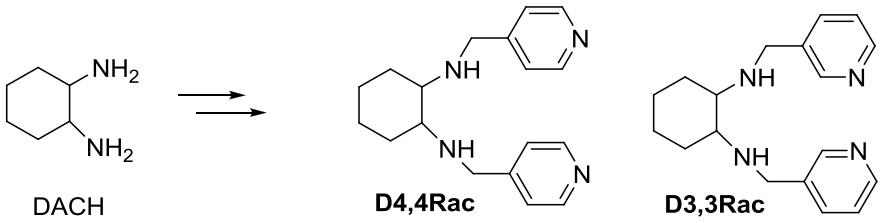


Figure 4-11. Prepared racemic 1,2-diaminocyclohexane-based compounds.

The general procedure of the synthesis of symmetric 1,2-diaminecyclohexane-based compounds (**D4,4; D3,3; D2,2** and **D4,4Rac; D3,3Rac**) used in this work, is presented on Figure 4-12. To a stirred solution of 2-or 3- or 4-pyridylcarboxaldehyde (2 eq.) in methanol, (1*S*,2*S*)- or racemic -1,2-diaminocyclohexane (1 eq.) in methanol was added slowly using a syringe pump. The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and further stirred for another 15 min. The mixture was filtered, and sodium borohydride (4 eq.) was added by portions over a period of 30 min. The mixture was refluxed for 1 h, and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure leading to a white solid. The solid was dissolved in water, followed by addition of KOH 1M solution to pH≥10 and successively extracted three times with dichloromethane. The combined organic layer was dried with Na_2SO_4, filtered and evaporated under reduced pressure, resulting in yellow oil with 75-95% yield. All compounds were purified by column chromatography on neutral SiO_2. After the column chromatography, the preparation of hydrochlorides with 3 eq. of 1M HCl was carried out. Hydrochlorides were dried under vacuum and recrystallized from *i*-PrOH giving a total yield of 30-60%.

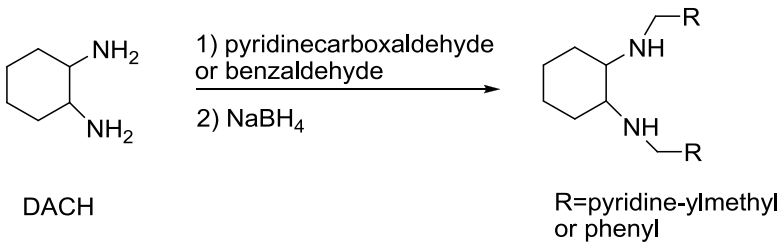


Figure 4-12. Synthesis of symmetric 1,2-diaminecyclohexane-based compounds.

X-ray analysis of crystals of diamine **D2,2** hydrochloride was done. In the asymmetric unit 2 molecules of diamine **D2,2**, 4 Cl^- anions and 3 water molecules are present. Positions of hydrogen atoms were unambiguously located by the presence of electron density. It is notable that only one of two secondary amines is protonated and only one of two pyridine rings. It was not evident before X-ray analysis, when was expected to see two same nitrogens protonated:

either two secondary amines or two pyridines. This is maybe the reason of fail to alkylate selectively pyridine rings (see part 4.2.4).

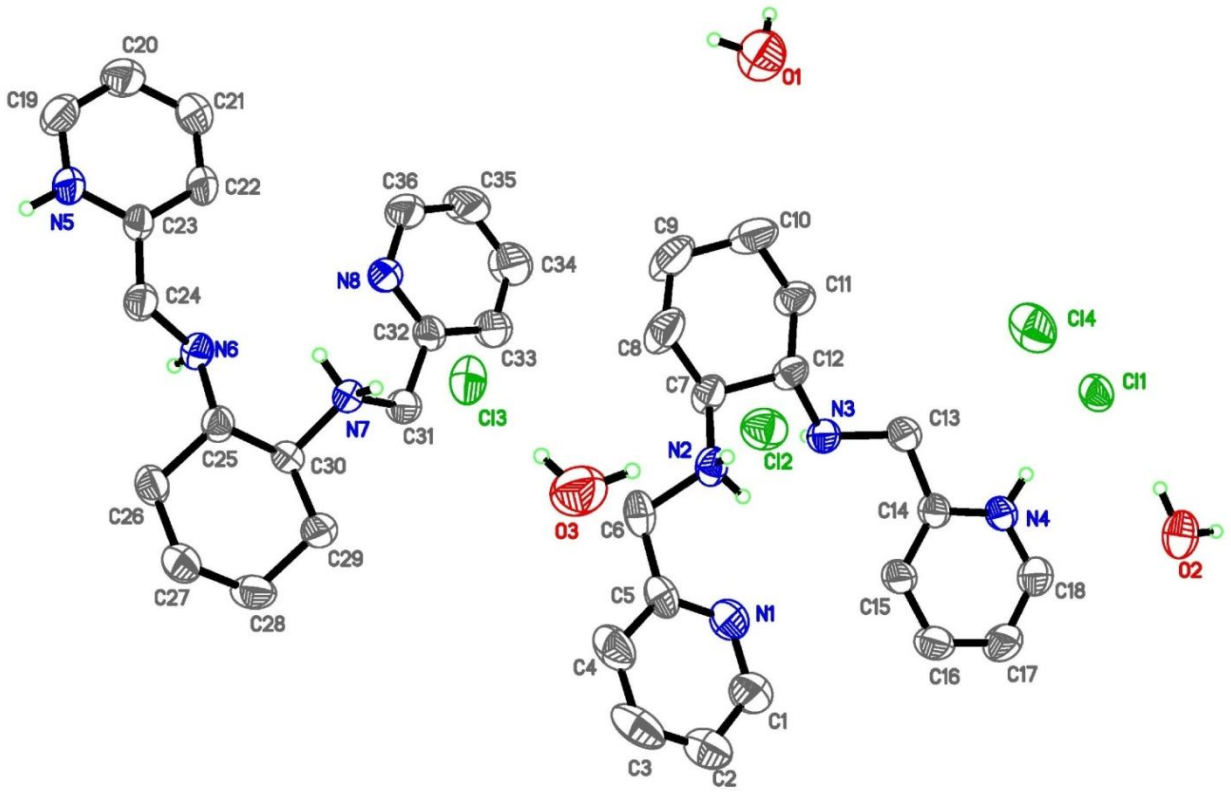


Figure 4-13. X-ray analysis of (1S,2S)-N1,N2-bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine dihydrochloride, 1½ H_2O ***D2,2-2HCl-½H_2O****. Ellipsoid drawing (50% probability).*

The synthesis of dissymmetric 1,2-diaminocyclohexane-based diamines consists of subsequently repeating of previously described strategy with two different aldehydes (Figure 4-14). Final compounds **D4,Ph; D3,Ph; D2,Ph; D4,3; D4,2** and **D3,2** were obtained after crystallization with an overall yield 20-40%.

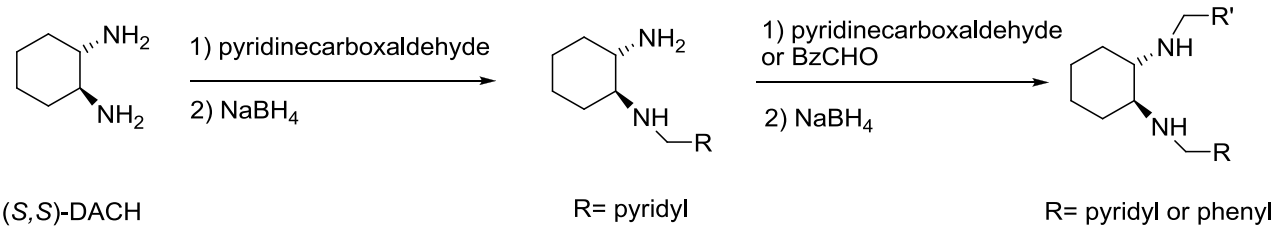


Figure 4-14. Synthesis of dissymmetric 1,2-diaminocyclohexane-based diamines.

All obtained diamines are stored as hydrochlorides to prevent degradation by air. Indeed, slow destruction was observed when diamines were stocked in free, not salt-like form.

4.2.3 Preparation of diamine-based ionic liquids

The concept of ionic liquid means that compound is ionic (containing ions, or saying another way having ionic bonds in its structure) and liquid at low temperatures. According to Peter Wasserscheid[12], an ionic liquid is a salt which has a melting temperature below the boiling point of water, 100°C. Rendering to this definition any kind of salt having melting temperature below water boiling point of 100°C can be called ionic liquid.

A commonly used method to make compounds ionic liquids is introduction to the molecule *n*-alkyl chains. But not only *n*-alkyl chains play a role in melting temperature decreasing, the anion also. Commonly used anions in ionic liquid chemistry are bis(trifluoromethanesulfonyl)imide $\mathbf{NTf_2^-}$, hexafluorophosphate $\mathbf{PF_6^-}$ and tetrafluoroborate $\mathbf{BF_4^-}$. These anions efficiently delocalize negative charge, lowering melting point.

It was decided to synthesize salts of different acids, commonly used to prepare commercial ionic liquids: hexafluorophosphoric acid HPF_6; tetrafluoroboric acid HBF_4; bis(trifluoromethanesulfonyl)imide $HNTf_2$. A collection of 6 diamine salts was prepared (Figure 4-15) starting from two diamines **D4,Ph** and **D4,4**. Physical properties of obtained products are compared in Table 4-2.

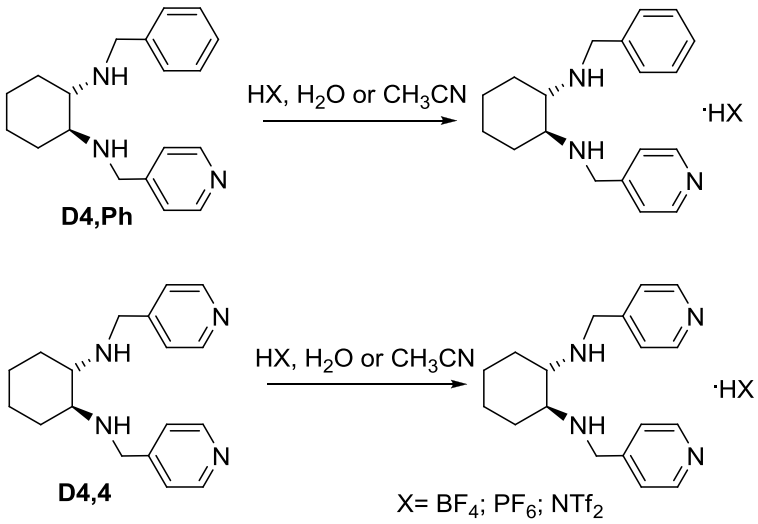


Figure 4-15. Protic diamine salts preparation.

Code	X	T_m or T_g, °C	$[\alpha]_D$, c=1 (MeOH)
D4,Ph-HPF$_6$	PF_6^-	-18.7 (T_{GT}) 79 (T_m)	+ 40.1
D4,4-HPF$_6$	PF_6^-	-19.1 (T_{GT}) 81 (T_m)	+ 41.7
D4,Ph-HBF$_4$	BF_4^-	99	+69.7
D4,4-HBF$_4$	BF_4^-	113	+58.5
D4,Ph-HNTf$_2$	NTf_2^-	0.3 (T_{GT})	+36.2
D4,4-HNTf$_2$	NTf_2^-	5.1 (T_{GT})	+58.5

Table 4-2. Protic diamine salts physical properties.

Two compounds from Table 4-2 are room temperature ionic liquids. Compound **D4,Ph-HNTf$_2$** has glass transition temperature +0.3°C and its structural analogue **D4,4-HNTf$_2$** has glass transition temperature +5.1°C. Visually they are represented as caramel-like yellow substances. Three others have melting temperatures below 100°C and can be considered as ionic liquids also.

Those kinds of low-melting point salts, having proton in the place of alkyl chain hydrogen atom, are called protic ionic liquids. All salts of HPF_6, HBF_4 and $HNTf_2$ acids show good correlation with theoretical expectations: all non-symmetrical **D4,Ph** diamine derivatives have lower melting temperatures that their symmetrical **D4,4** diamine analogues. Also, NTf_2^- was the best choice to create ionic liquids, what is coherent with general observations of ionic liquid properties. The preparation method was scaled up to multigram scale and produced compounds, which were used in ELLEs.

X-ray analysis for the compound **D4,Ph-HBF$_4$** from Table 4-2 was possible, because it forms colorless monoclinic crystals in water. It was found the traces of water, ½ molecule to one molecule of compound. The exact position of water hydrogens was not determined. It is necessary to note that secondary amine is protonated, and not the pyridine nitrogen (Figure 4-16).

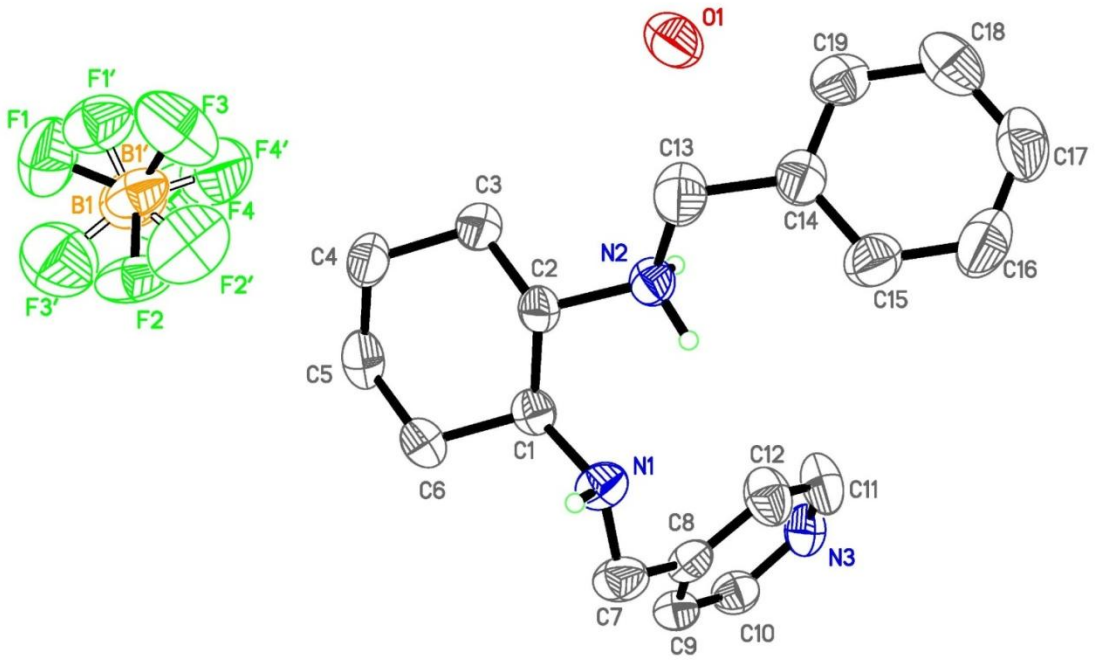


Figure 4-16. X-ray structure compound ***D4,Ph-HBF4****. Ellipsoid drawing (50% probability).*

^{1}H NMR study was performed to determine the preferential position of protonation of diamines in solution. Using hydrochloric acid to prepare mono-, bis- and trihydrochlorides of **D4,Ph**-diamine (Figure 4-17). It was shown that at first HCl protonates the secondary amine function, then the second secondary amine function, and finally, aromatic atom of nitrogen (Figure 4-18). We explain this as follows: when adding to the starting diamine (Figure 4-18a), first equivalent of HCl protonates one of the secondary amines and this causes splitting of signal of two protons situated in positions 9 and 10 close to secondary amines (Figure 4-18b). Second added molecule of HCl protonates another secondary amine function, making the chemical shifts of protons 9 and 10 similar (Figure 4-18c). Finally, third equivalent of HCl protonates pyridine's nitrogen thus making the chemical shifts of protons 9 and 10 slightly different (Figure 4-18d).

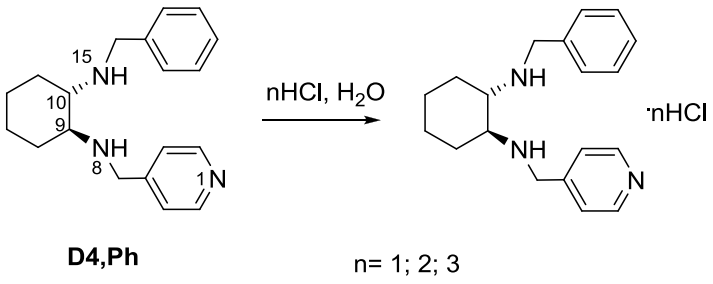


Figure 4-17 Preparation of mono-, bis- and trihydrochlorides of ***D4,Ph****-diamine.*

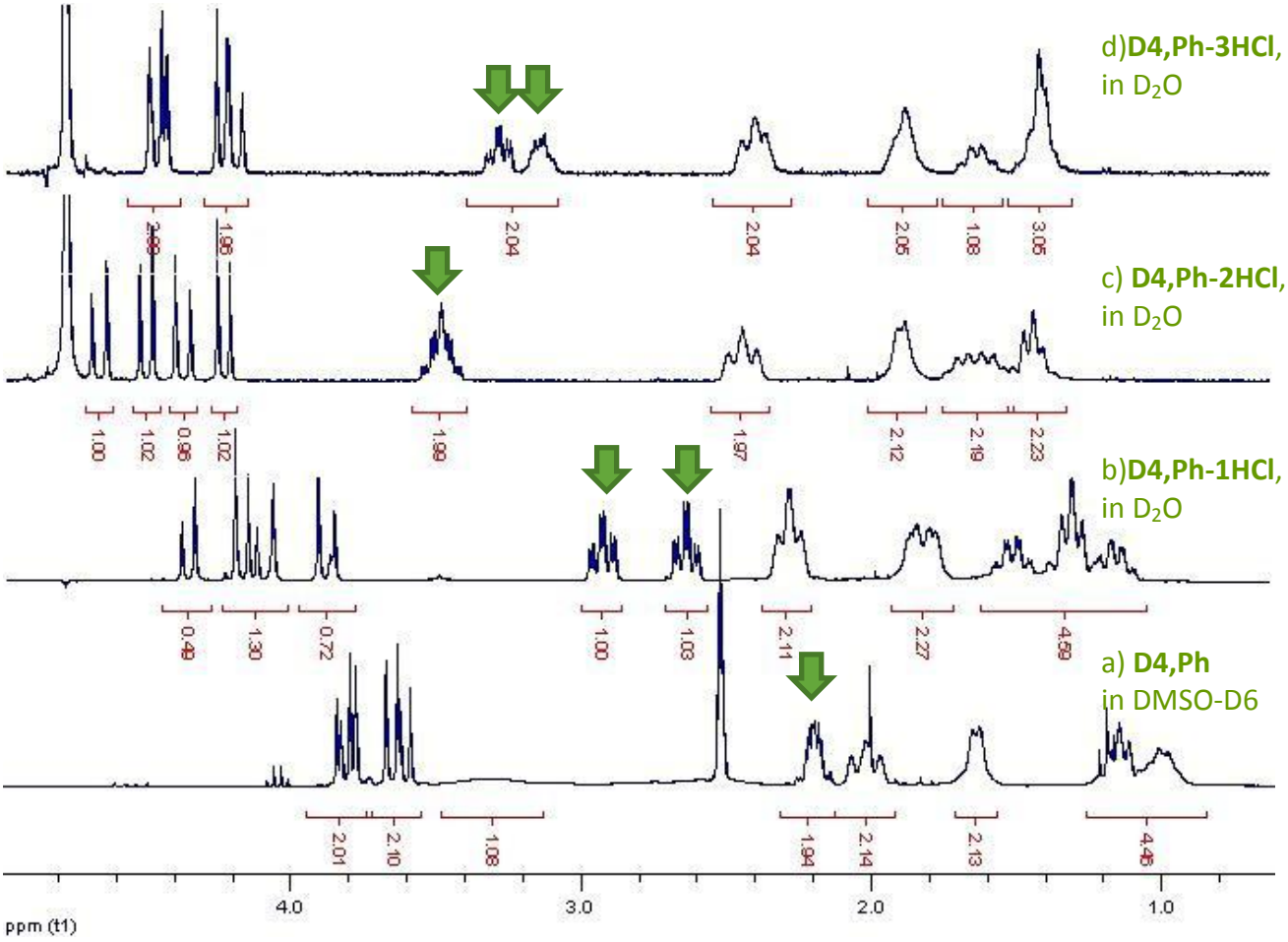


*Figure 4-18. NMR ^1H study of mono-, bis- and trihydrochlorides of **D4,Ph**-diamine.*

This observed comportment in solution for **D4,Ph**-diamine hydrochlorides is different to that of structure **D2,2-2HCl-½H$_2$O** (Figure 4-13), X-ray analysis of which showed that in the presence of 2HCl only one of secondary amines is protonated and only one of two pyridine rings. Exact position of proton (which atom of nitrogen is protonated), when these compounds are dissolved in ionic liquids, was not determined yet. It is possible that proton in ionic environment can pass from aliphatic to aromatic nitrogen atom. In this case, properties of protonated molecule will change also.

4.2.4 Alkylation of cyclohexanediamine-based diamines

Widespread method to decrease melting point of ionic compounds is alkylation of nitrogen (phosphorus or sulfur) with *n*-alkyl halides. Alkyl chains create a distortion of the crystal mesh, leading to a decrease in melting temperature.

One of the goals of this project was to find suitable synthetic methods to prepare the new class of chiral ionic liquids: benzathine-like, *trans*-1,2-diaminocyclohexane-based. To meet this goal, was planned to alkylate prepared (1*S*,2*S*)-diaminocyclohexane-based compounds (Figure 4-10) and follow all alkylations by ion metathesis (Figure 4-19).

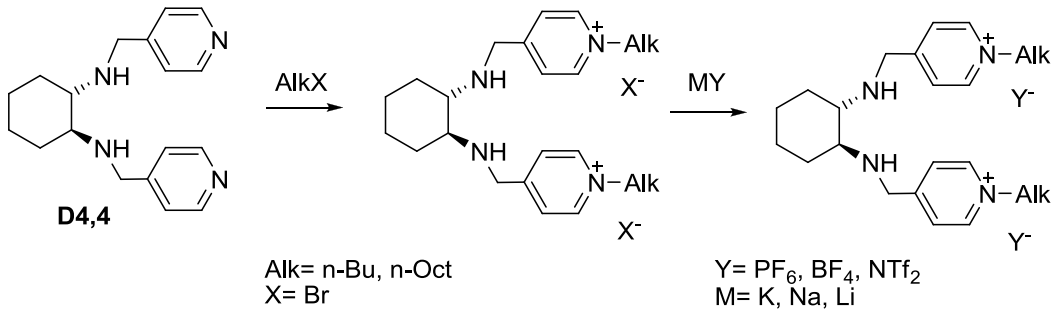
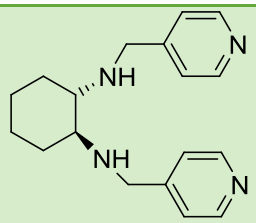
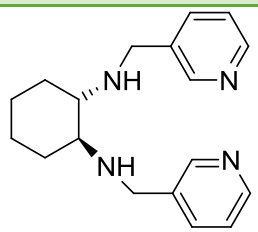


*Figure 4-19. Planned synthetic way to prepare chiral ionic liquids: example for compound **D4,4**.*

We started the study of chemical properties by molecules **D4,4** and **D3,3**. Great number attempts of alkylation of these compounds were carried out without success. Every time was obtained either complicated mixture of different alkylated products, where desired compound was not major, or no reaction was observed at all. Table 4-3 unites all details of performed alkylations.

Alkylated product	Alkylation agent	Reaction conditions	Result
 **D4,4**	C_4H_9Br, 2 eq.	75°C, CH_3CN, 2h	No reaction
	C_4H_9Br, 1 eq.	85°C, CH_3CN, 2h	No reaction
	C_4H_9Br, 1 eq.	80°C, w/s, 2h	Destruction of starting compound
 **D3,3**	MeI, excess	40°C, w/s, 4h	Multiple alkylations
	MeI, 3 eq.	40°C, CH_3CN, 12h	Multiple alkylations
	MeI, 3 eq.	40°C, CH_3CN, 4h	Multiple alkylations
	MeI, 0.5 eq.	rt, CH_3CN, 4h	Multiple alkylations
	$C_8H_{17}Br$, 1 eq.	80°C, w/s, 24h	Destruction of starting compound and ≈ 15% of alkylation

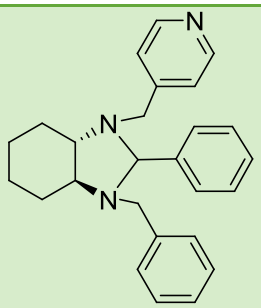
 **D2,Ph,Ph**	*i*-PrI, 1 eq.	30°C, CH_3CN, 12h	No reaction
	i-PrI, 1 eq.	30°C, CH_3CN, 48h	≈ 25% of alkylated compound after deprotection by HCl
	i-PrI, 1 eq.	100°C, CH_3CN, 12h	Destruction of starting compound

Table 4-3. Attempts of alkylation of 1,2-diaminocyclohexane-based compounds.

A possible reason of fail to alkylate selectively pyridine rings may be that the reactions of aliphatic nitrogens with alkylation agents. Compounds **D4,Ph** and **D2,2** were modified to protect both secondary amine functions via aminals formation (Figure 4-20).

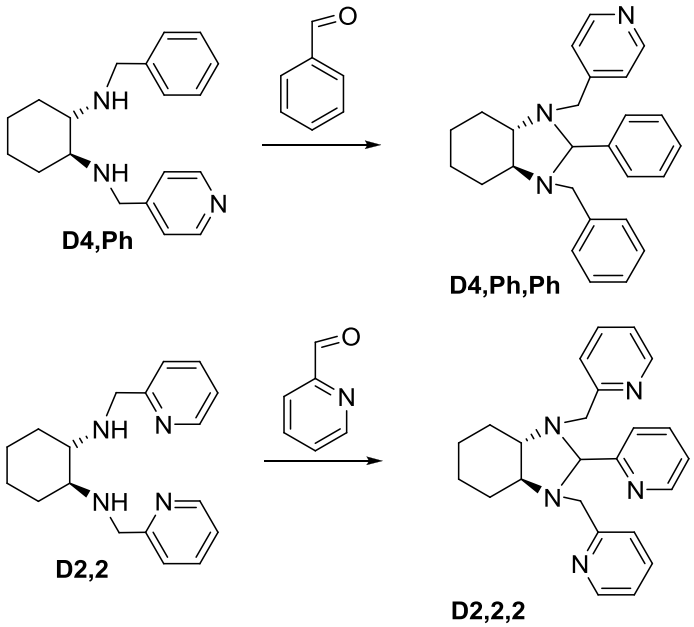


*Figure 4-20. Synthesis of aminals **D4,Ph,Ph** and **D2,2,2**.*

Compound **D4,Ph,Ph** was used as alkylation substrate and showed 25% overall yield (Figure 4-21), which was considered not enough good to meet our goals.

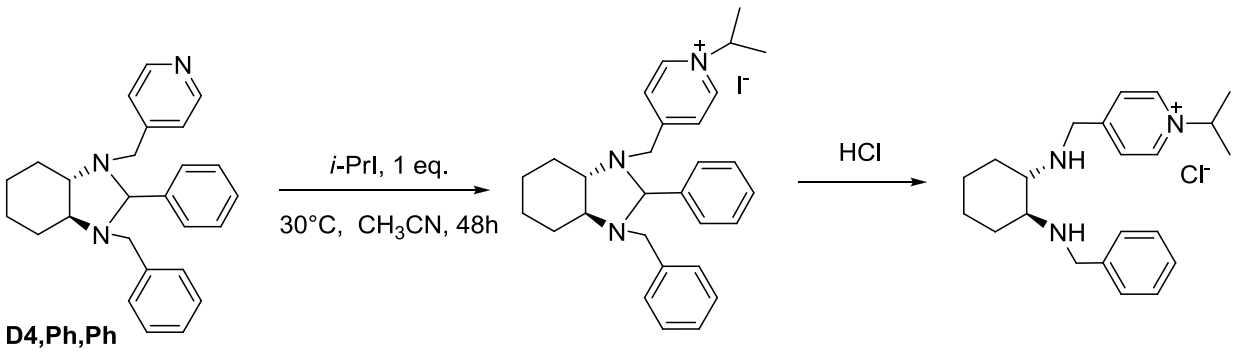


*Figure 4-21. Alkylation of compound **D4,Ph,Ph** followed by deprotection of secondary amines.*

To resolve the problem of alkylation fail and to find the simplest way for this, we passed to the series of model reactions.

4.2.5 Searching for alternative way for alkylated diamines

The initial goal of these reactions was to find simple synthetic way to alkylate pyridiniums without touching secondary amine functions to be able to produce a new class of chiral ionic liquids based on 1,2-diaminocyclohexane. These chiral ionic liquids were planned to be used in ELLEs as chiral resolvers.

The idea was to alkylate the pyridine-carboxyaldehydes, and make reductive amination afterwards. This way might avoid non desired alkylations of secondary amine functions in final product. Simple "model" compounds were chosen to verify the feasibility of this synthetic way (Figure 4-22).

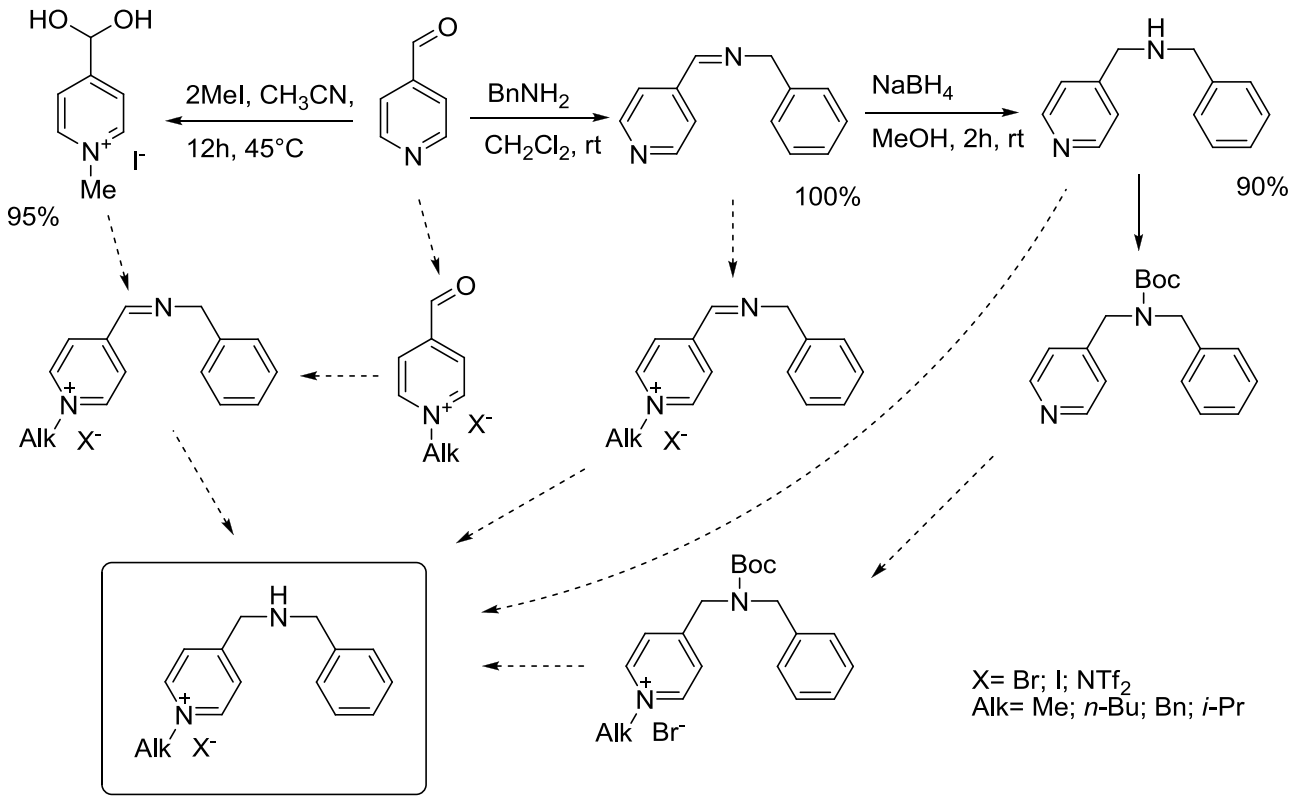
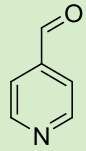
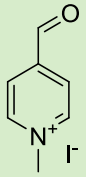
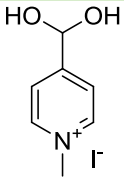
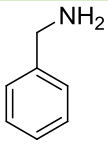
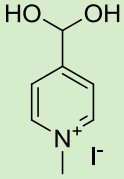
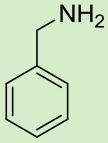
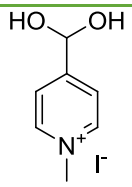
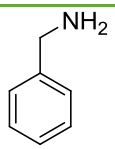
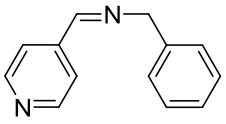
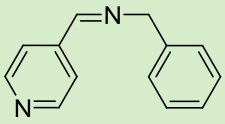
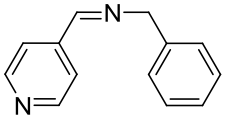
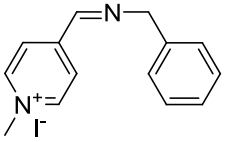
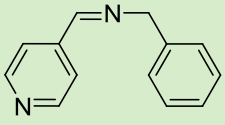
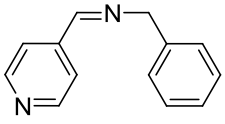
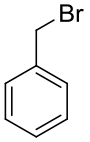
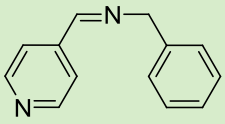
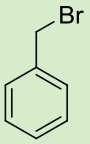
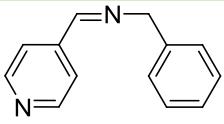
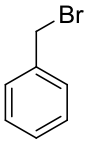
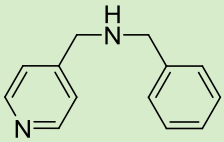
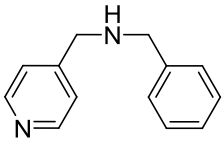
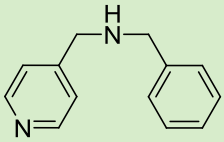
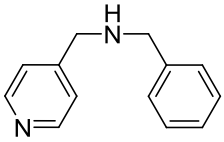
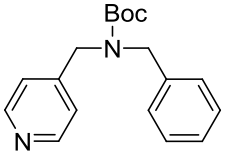


Figure 4-22. Synthetic pathway, which was tested.

The conditions and results of all unsuccessful reactions are united in Table 4-4.

Reagent 1	Reagent 2	Reaction conditions	Result	Yield
	MeI	CH_3CN, 36h, rt		30 %
		CH_2Cl_2, rt	Complex mixture	-
		1) CH_2Cl_2, Na_2SO_4 2) $NaBH_4$	Complex mixture	-

		CH_2Cl_2, Na_2SO_4	Demethylation 	nd
	MeI	CH_3CN, 12h, 40°C	Destruction of starting compound	-
	MeI	w/s, 12h, 40°C		7%
	*i*-PrI	CH_2Cl_2, 12h, 30°C	No reaction	-
		MeOH, 12h, rt	Complex mixture	-
		Et_2O, 8h, 30°C	Complex mixture	-
		CH_2Cl_2, 16h, rt	Complex mixture	-
	*n*-C_4H_9Br	Acetone, 12h, 50°C	No reaction	-
	MeI	CH_3CN, 8h, 50°C	Complex mixture	-
	MeI	Acetone, 8h, 50°C	Complex mixture	-
	Boc_2O	EtOH absol, 12h, rt		Self-deprotection under purification

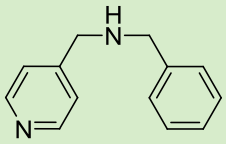
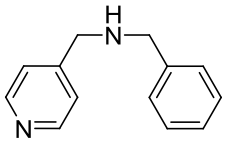
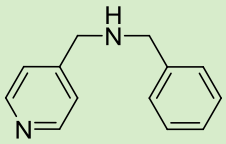
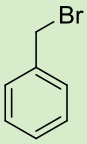
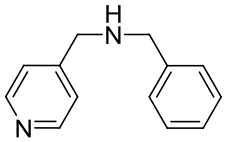
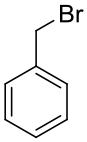
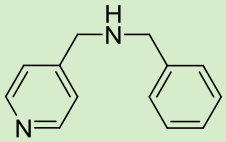
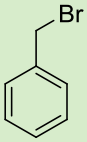
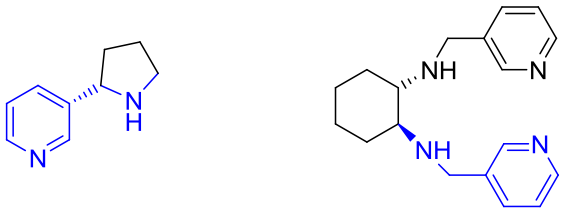
				conditions
	$MeNTf_2$[110]	$CHCl_3$, 12h, rt	No reaction	-
	*i*-PrI	w/s, 12h, 40°C	Destruction of starting compound	-
		MeOH, 12h, rt	Formation of two alkylated products	-
		Et_2O, 8h, 30°C	Complex mixture	-
		CH_2Cl_2, 16h, rt	Complex mixture	-

Table 4-4. Results of model reactions.

Finally, it was shown that there is no simple way to reach pyridine-alkylated compounds, containing secondary amine function. It can be explained by the competition between two nitrogen atoms while a compound containing both of them undergo alkylation by halogeno alkanes. This supposition is supported by the X-ray analysis of compound **D2,2-2HCl-½H_2O** (Figure 4-13). It was found that only one of two secondary amines is protonated and only one of two pyridine rings (see Figure 4-13 and the related text). Before the X-ray analysis it was expected to see two same nitrogens protonated: either two secondary amines or two pyridines.

In the literature it is known that alkylation of molecules bearing two different nitrogen atoms causes problems[111]. When trying to alkylate selectively the nicotine (Figure 4-23), literature disagrees which of two atoms is alkylated first, mainly producing mixtures of alkylated products. The reaction conditions from successful examples of alkylation of nicotine were applied for our diamines, but without success (see Table 4-3).



(*S*)-nicotine **D3,3**

Figure 4-23. (S)-nicotine. Similar structural part with our compound ***D3,3*** *is highlighted in blue.*

In the same time, the idea to alkylate the pyridine-carboxyaldehydes, and make reductive amination afterwards was not neither productive.

Other productive ways can be proposed to achieve the desired alkylated product. For example, Mitsunobu coupling[112] between alkylated pyridine-methanol, or protection of secondary amine function by another protective group than Boc to prevent undesirable alkylation. But as soon as simple synthetic way was not found and searching for it could be delayed for unknown period of time, it was decided to concentrate our activities on ELLEs – the main reason of this work.

4.2.6 Synthesis of tartaric acid based compounds

Tartaric acid is naturally occurring compound, with low toxicity (LD_{50} is about 7.5 grams/kg for a human). That is why CILs derived from tartaric acid represent the area of interest in the green chemistry research. Our attention was focused on the use of tetrabutylphosphonium tartrates like chiral selectors in ELLEs, and it was shown that our choice was correct (see part 4.7).

The synthesis of CILs from tartaric acid and tetrabutylphosphonium hydroxide is quite simple, and consists of mixing two water solutions of commercially available compounds (Figure 4-24). Along with two chiral compounds based on (*R,R*) and (*S,S*) tartaric acid, *meso* and racemic tartrates were prepared.

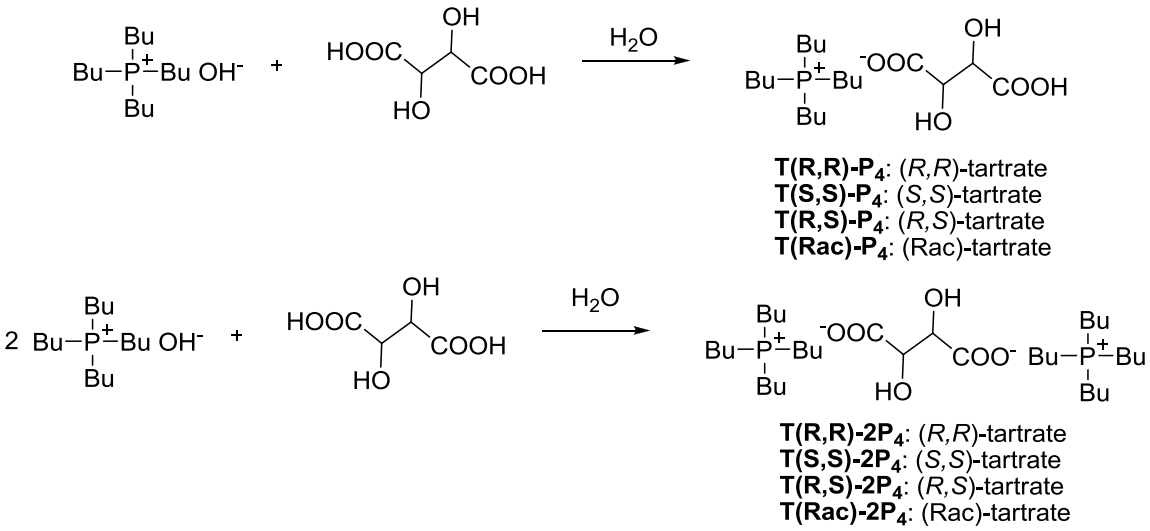


Figure 4-24. Synthesis of CILs from tartaric acid and tetrabutylphosphonium hydroxide.

Simple from the first view, those syntheses contained pitfalls. The difference in chemical shifts of the α-protons in the starting acid and the resulted CILs were not enough significant to distinguish monosubstituted product from bis-substituted. Butyl chains in tetrabutylphosphoniums connected with different anions give the same signals, as well as phosphorus in ^{31}P NMR spectra. So, little information about the product purity could be obtained by NMR.

During the study of the partition of **[PBu_4]-[(*L*)-Trtr]** in water/CH_2Cl_2 and in water/$CHCl_3$ biphasic mixtures it was found that from 15 to 20 wt% of ionic liquid distributes to organic phase, and this distribution happens only during the first extraction, when all following extractions are not able to extract anymore. ^1H NMR study of the extracted compound showed the presence of tetrabutylphosphonium but without tartaric acid. It was proposed that extracted compound represents the residual tetrabutylphosphonium chloride or bromide, which was used in the preparation of [PBu_4]OH. Indeed, it was proven by the Beilstein test, which was positive for extracted compound, for starting IL and for tetrabutylphosphonium hydroxide, but negative to the extracted water solution of IL (extracted 4 times with CH_2Cl_2 or $CHCl_3$ and dried under reduced pressure to eliminate the traces of organic solvents).

This discovery helped us to understand the strange behavior of tetrabutylphosphonium tartrates when trying to examine their physical properties. Finally, commercial [PBu_4]OH was purified from tetrabutylphosphonium halides by multiple extraction with CH_2Cl_2 and drying under reduced pressure. To determine the exact concentration of [PBu_4]OH, it was titrated with 1M HCl to define the concentration and verified with the Beilstein test to confirm the absence of halogens.

There are about 1000 different phosphonium salts reported in the literature. Our discovery of the purity determination problem points out the importance to make attention on the product characterization methods when taking the data from previous researches. From the beginnings of the organic chemistry, elemental analysis stays the simplest and very efficient way to ensure the purity of the product and must be taken into account when working with ILs.

The problem of non-reproducibility of the literature data for ILs was discussed recently in the article "*Purity specification methods for ionic liquids*". In this work the authors note that little attention has been paid to the characterization of the purity of ILs. ILs impurities can residue from unreacted starting material, by-products (amines, alkylating agents, inorganic halides), solvents, water and decomposition products. The authors compiled a number of analytical protocols (with their detection limits) and quantitative methods for the determination of the total ionic liquid content[113].

At the beginning of this work no tetrabutylphosphonium tartrates were known. Two bis(tetrabutylphosphonium) tartrates (**[PBu_4]-[(*L*)-Trtr]** and **[PBu_4]$_2$-[(*L*)-Trtr]**) were reported in 2009 as colorless liquids and they were characterized only by NMR [92]. In our work these compounds were obtained as pale-yellow liquids before the purification of the starting material from tetrabutylphosphonium halides, and as white waxes after it. It allows us to suppose that reported compounds were not individual substances.

In this work the collection of 2 mono- and 2 bis(tertrabutylphosphonium) tartrates ((*R,R*) and (*S,S*)) was prepared with the goal to try them as chiral hosts in ELLEs. The observed results are very encouraging and discussed in details in the part 4.7.2.

Another series of salts: 6 prolinium tartrates were prepared (Figure 4-25) with the goal to check possible enantiomeric interactions by ^{1}H and ^{13}C NMR study. No differences between racemic proline tartrates and enantiopure proline salts were found by ^{1}H and ^{13}C spectra analysis of all prolinium tartrates in deuterated water and methanol. The absence of interaction can be explained by stronger solvation effects between proline and tartaric acid and solvent, that ion pairing between two different enantiomers of proline and tartaric moiety.

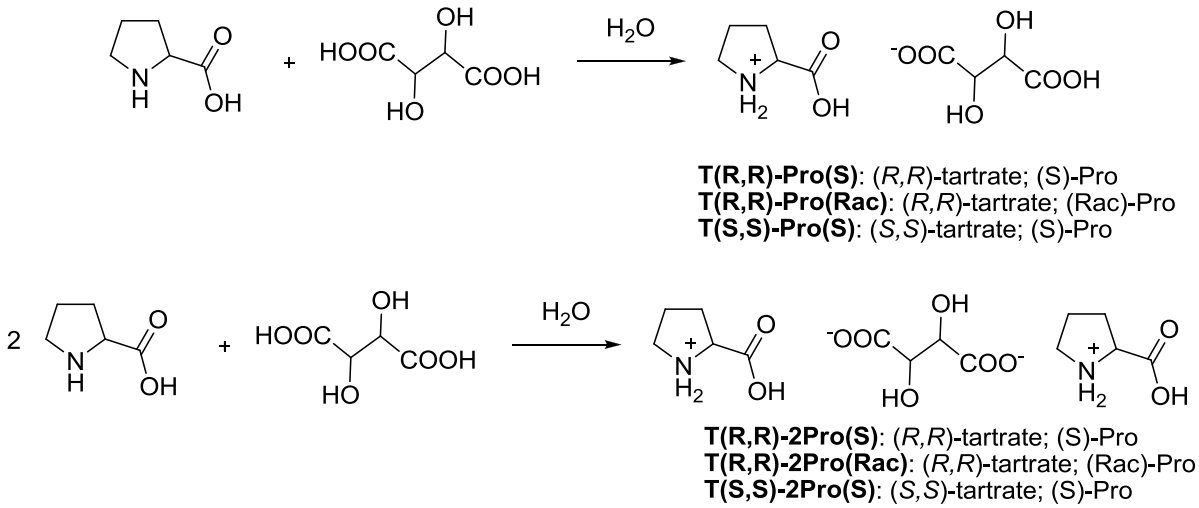
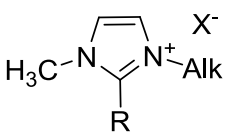


Figure 4-25. Synthesis of prolinium tartrates.

4.3 Choice of co-solvent ILs

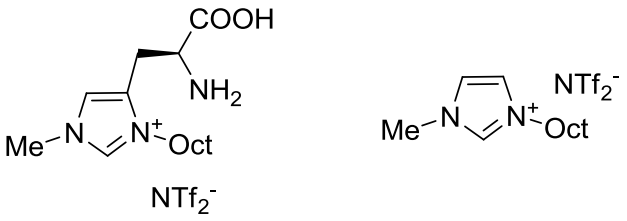
CILs can be used simultaneously as a solvent and chiral selector. But we decided to dissolve them in commercially available ILs due to some limitations of CILs as high viscosity and their cost. Almost all chosen CILs were too viscous to be mixed by the magnetic stirrer. Also, in order to be able to separate the two phases, the minimal volume about 1 mL of the two liquids was required. Diluting our CILs in commercially available ILs makes possible to save precious chiral hosts, to make the system less viscous and to reduce possible errors by operating with larger volumes of liquids. Another reason to dilute CILs was related to the fact that in all known examples of ELLE in literature chiral hosts were dissolved in a solvent (which is frequently hydrophobic). In total, 5 ionic liquids were chosen to play the role of co-solvent IL (Figure 4-26).



[bmim]NTf_2 : Alk= *n*-Bu; X= NTf_2; R= H
[b2,3mim]NTf_2 : Alk= *n*-Bu; X= NTf_2; R= Me
[omim]NTf_2 : Alk= *n*-Oct; X= NTf_2; R= H
[bmim]BF_4 : Alk= *n*-Bu; X= BF_4; R= H
[bmim]PF_6 : Alk= *n*-Bu; X= PF_6; R= H

Figure 4-26. Co-solvent ILs.

General strategy to choose co-solvent IL was to make it maximum similar to the CIL it is used together. That means to use one IL with the same alkyl chain and the same anion. For example, for [omHis]NTf_2 **H6b** the co-solvent IL was [omim]NTf_2 (Figure 4-27).



H6b [omHis]NTf_2 [omim]NTf_2

*Figure 4-27. CIL [omHis]NTf_2 **H6b** was used with the co-solvent IL [omim]NTf_2.*

For dodecyl-containing CILs were used octyl-containing ILs with the goal to reduce viscosity of the final system. Sometimes, for the same reason, *n*-butyl-alkylated ILs were applied together with octyl-containing CILs. When the needed IL was not available from the supplier they were prepared in amount of dozens of grams using common technique of alkylation and metathesis (Figure 4-28). In total, 2 ILs were prepared to be used as co-solvent in ELLEs.

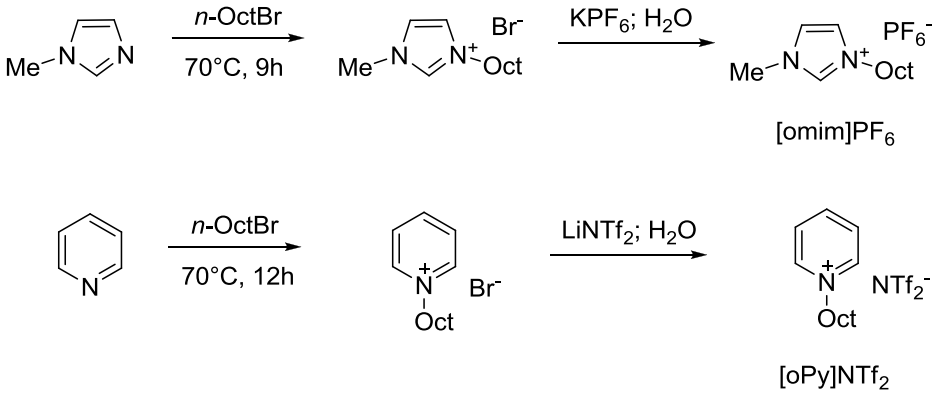


Figure 4-28. Synthesis of co-solvent ILs.

4.4 Choice of the second solvent for biphasic system

Indispensable condition for ELLE is the presence of two (at least partially) immiscible liquids. As our substrate, host and the first solvent were already known, so it was simple to choose the second solvent to complete our ELLE system.

As our racemic compounds were polar, and CILs along with co-solvent ILs were hydrophobic, the second solvent to create biphasic system was chosen to be water. This choice was suitable for us also because water is one the greenest solvents to be combined in one application together with ILs.

One exception was the pipecoloxylidide. In the form of free base it was not soluble in water, so toluene was used in the early tests. But after discovery of the cross-metathesis (*vide infra* 4.7) toluene was successfully replaced to water.

4.5 Solubility tests of chosen substrates

Before starting the screening of chiral discrimination power of chosen CILs towards racemic substrates, it was necessary to check their behavior in the chosen biphasic system of co-solvent IL/water. It was important to check the capacity of chosen IL to dissolve CILs and racemic substrates. If they were soluble, those solutions were extracted by water to ensure the possibility of IL to keep CIL when releasing only racemic substrates.

Amino acids are possible to be extracted from water to ILs, as was shown by numerous studies (see part 3.2). Pipecoloxylidide was not soluble in water and soluble in chosen ILs. Another solvent was needed to extract pipecoloxylidide from its solution in ILs. This solvent was important to be immiscible with chosen IL at least partially and able to dissolve pipecoloxylidide. Toluene seemed to be the best candidate for this purpose, but as it was mentioned above, it was quickly replaced to water.

Chiral ionic liquids (Figure 4-2) showed to be suitable for ELLEs but with some limitations to each family. Histidiniums **H5-H6** (Figure 4-9) were shown to be soluble in pure water at pH values different from neutrality. But in the presence of hydrophobic IL stay in it instead of water. DACH-based ionic liquids (Figure 4-15) are slowly soluble in pure water, and in the presence of hydrophobic IL dissolve themselves in it. Tartaric-acid based CILs (Figure 4-24) are highly hydrophilic substances despite the presence of hydrophobic tetrabutylphosphonium part. When dissolved in hydrophobic IL and extracted by water, cross-metathesis phenomenon was observed: highly hydrophilic ions (tartaric acid and imidazolium) unite together in water, while hydrophobic ions (tetrabutylphosphonium and NTf_2^-) unite in IL. This (at first unexpected) logic behavior of ILs was investigated in details and shown to be suitable for ELLE in ILs (see part 4.7). Finally, phenylethylamine-based CIL was hydrosoluble, but in the presence of hydrophobic IL partition to it.

Anyway, adding racemic substrate to the solution of CIL in mixture IL/water can provoke unexpected salting-in and salting-out effects, changing solubility behavior of all compounds in the system. So it was decided to pass directly to enantioselective extractions.

4.6 Screening of all substrates with all hosts

One liquid-liquid extraction is the virtual equivalent of one chromatographic stage. In fact, one chromatographic stage (plate) represents equilibrium state between the selector and analyte, when one compound (or enantiomer) interacts with the substrate stronger than another, making the complete separation possible after several stages (plates). The number of necessary stages is dependent mainly on the difference in interaction forces between the two separated compounds.

Other factors influencing extraction include: mechanism of extraction (ion exchange or complexation), host concentration, host/racemate ratio, salting-in and salting-out effects, pH, operating temperature and pressure, time of extraction and time of equilibration, choice of solvents pair, interfacial tension and phase density difference, emulsification and scum-formation tendency, type of chosen extractor, extractor size and horsepower requirement, etc.

The number of factors responsible for the success of ELLE process is so large that it was impossible to predict the best combination of all of them. Also it was not the main problem because at the beginning of our work we were not sure about the chiral discrimination capabilities of our CILs to resolve racemic substrates. So it was decided to make screening of all available chiral hosts with all chosen racemic substrates to choose the best combination with the highest ee and yield and then to continue to study the role of important parameters on the chosen system.

The biphasic chiral extraction system was established by adding ½ equivalent of chiral ionic liquid to 10 equivalents of commercial hydrophobic ionic liquid. Ionic liquid phase was enriched by 1 equivalent of racemic compound to be resolved and the system was stirred for 12 hours at normal conditions to let molecules of host and racemate interact. After that 100 equivalents of water (or 40 equivalents of toluene for pipecoloxylidide) were added and the biphasic system was stirred for additional 3 hours with the goal to extract one of enantiomers. Water (or toluene) layer was separated, evaporated and dried under vacuum line (Figure 4-29).

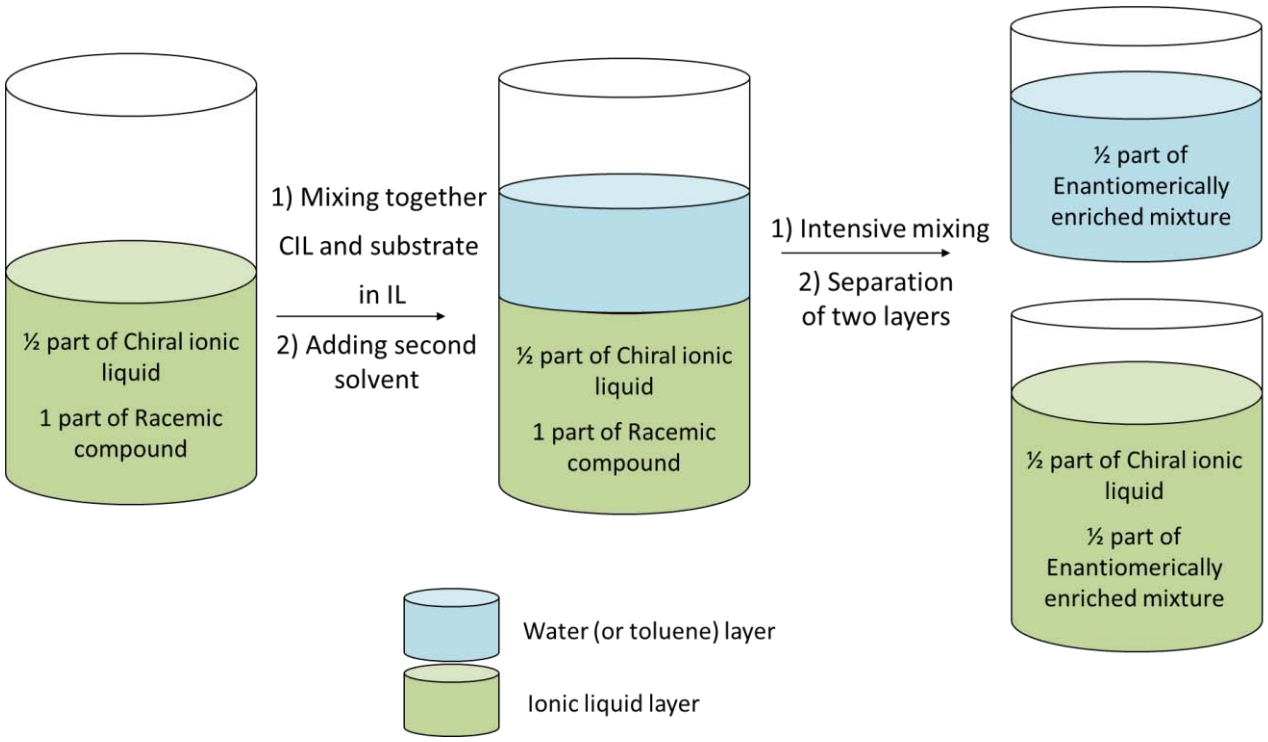
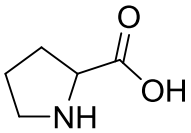
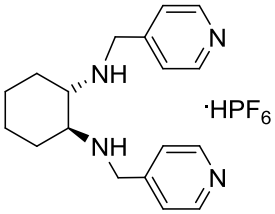
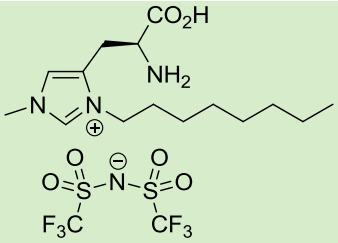
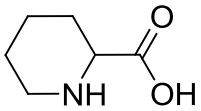
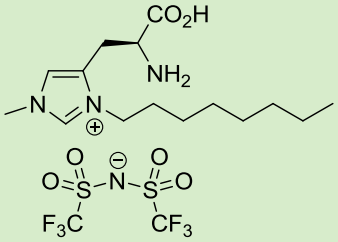
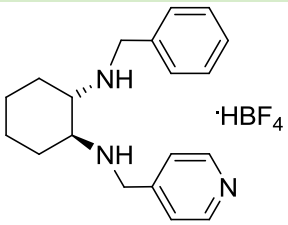
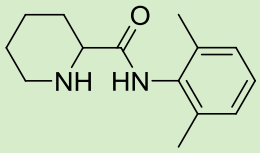
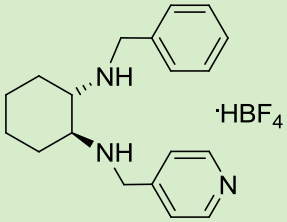
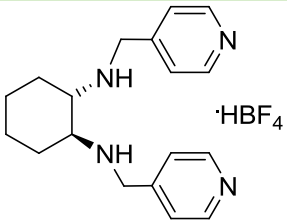
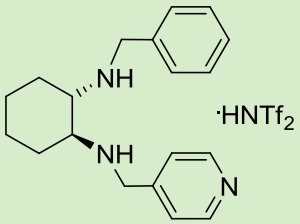
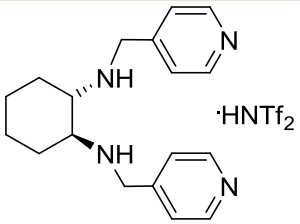
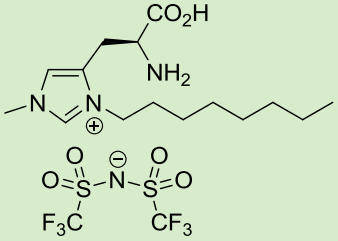


Figure 4-29. Schematic representation of ELLE using chiral ionic liquids.

The equilibrium experiments were performed in 5 mL stoppered tubes. The quantity of IL and water was chosen to be about 1 mL and 0.2 mL of aqueous (or toluene) layer. It was necessary to choose the appropriate volume to make two layers separable using common laboratory techniques. Smallest volume of water is difficult to separate manually and larger volumes require more precious starting materials. When no clear phase boundary was visible, we centrifuged for 15 minutes at 1000 rpm with cooling to 5°C to increase IL viscosity. Separated layers were analyzed: mass yield and enantiomeric excess were determined. For quantitative measure of enantiomeric excess chiral HPLC was used. Detailed descriptions of HPLC conditions for each used substrate are described in the part 6.1.

All 56 possible combinations were checked (4 racemic substrates and 14 CILs). Each extracted residue was weighted and analyzed for enantiomeric excess using chiral HPLC. When no ee was determined or no substrate was extracted - no further investigation of those extractions was done. But when ee exceeded 3%, ^{1}H NMR analyses were applied to determine the composition of the extracted mixture. Using ^{1}H NMR spectra approximate content of substrate in the mixture was determined (because sometimes little amount of IL was extracted together with the substrate) and α_{op} was calculated (for α_{op} meaning see Equation 3-2). The results for the best candidates are summarized in Table 4-5.

CIL	Conditions	% of initial mass	% in extracted mixture	ee	α_{op}
Racemic substrate to be resolved (1 eq.) 					
 **D4,4-HPF$_6$ 0.5 eq.**	[bmim]PF$_6$ 5 eq.; Mixing 3h; RT; Water, 25 eq.; Extraction 12h.	58	77	**14%**	**1.90**
 **0.5 eq.**	[omim]NTf$_2$ 5 eq.; Mixing 3h; RT; Water, 25 eq.; Extraction 12h.	51	44	**12%**	**1.53**
Racemic substrate to be resolved (1 eq.) 					
 **H6b 0.5 eq.**	[omim]NTf$_2$ 5 eq.; Mixing 3h; RT; Water, 25 eq.; Extraction 12h.	40	44	**8%**	**1.31**
 **0.5 eq.**	[bmim]BF$_4$ 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	19	2	**10%**	**1.28**

Racemic substrate to be resolved (1 eq.) 					
CIL	Conditions	% of initial mass	% in extracted mixture	**ee**	**α_{op}**
 **D4,Ph-HBF_4 0.5 eq.**	[bmim]BF_4 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	19	33	**4%**	**1.10**
 **D4,4-HBF_4 0.5 eq.**	[bmim]BF_4 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	16	38	**5%**	**1.12**
 **D4,Ph-$HNTf_2$ 0.5 eq.**	[bmim]NTf_2 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	12	23	**2.5%**	**1.05**
 **D4,4-$HNTf_2$ 0.5 eq.**	[bmim]NTf_2 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	14	21	**3.5%**	**1.08**
 **H6b 0.5 eq.**	[bmim]NTf_2 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	10	24	**3%**	**1.06**

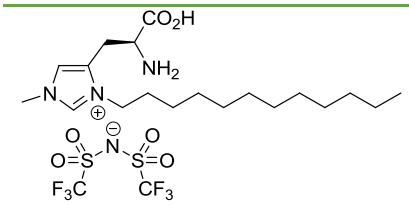
 **H6c 0.5 eq.**	[bmim]NTf_2 10 eq.; Mixing 12h; RT; Toluene, 40 eq.; Extraction 5h.	1.5	16	**11%**	**1.25**

Table 4-5. Best examples of screening of all substrates with all hosts.

As it shown in the Table 4-5, three compounds (proline, pipecolinic acid and pipecoloxylidide) showed remarkable results with ees in range of 10-14%. But proline and pipecolinic amino acids were rejected from the future series of tests due to the problems with precise determination of ee using chiral HPLC. It happened because the concentration vs. response of ELS detector is not linear over the solute's concentration range. So it was not always possible to be completely sure in results for proline and pipecolinic acid. Silaproline was rejected because no ee was observed during the tests.

Interesting to note that in the series of DACH-based CILs PF_6^--containing compounds **D4,4-HPF$_6$** shows ee only once, when BF_4^- and NTf_2^- -containing compounds **D4,4-HBF$_4$; D4,Ph-HBF$_4$; D4,4-HNTf$_2$** and **D4,Ph-HNTf$_2$** were proved to be more reliable chiral resolvers. To check the resolving power of DACH-based hydrochlorides, all 13 available compounds (see part 6.3) were tested under the same conditions with pipecoloxylidide and showed no chiral discrimination activity. It can be explained by the favorable influence of the anions which are able to delocalize effectively negative charge.

Also it is important to note that in the series of histidiniums **H5-H6** only those bearing carboxylic acid function show chiral discrimination activity. Methyl esters are not active and this can be explained by the impossibility of ion pairing between methyl ester and amines.

The maximal ee was observed with the most hydrophobic compound bearing α-amino acid function. This result correlates well with theoretical expectations: more hydrophobic host will retain better in the hydrophobic medium.

All operational selectivity α_{op} vary from 1.05 up to 1.25 and are lower than 1.50, value required for the development of the process. But they are the first examples of ELLE in IL media using CILs as chiral selectors and without the mediators of complexation as metals ions. These first results are very promising and show that the initial idea of this work is correct and productive.

Another process was shown to be effective in ELLE in ILs: cross-metathesis.

4.7 Cross-metathesis

During the solubility tests of the **$[PBu_4]_2$-[(*R,R*)-Trtr]** in [bmim]NTf_2/water system it was observed that the tartaric acid partitions quantitatively to water because of its highly hydrophilic nature. As the charge balance of two phases must be respected the tartaric acid bis-anion partitions together with two cations. Interesting to note, that those cations are not initial tetrabutylphosphoniums, but another, more hydrophilic cations present in the mixture. In our example they were imidazoliums, because they are more hydrophilic that tetrabutylphosphoniums. The exchange is complete, i.e. we extract equivalent quantity of cations to ensure the electroneutrality of the solution.

We understand this as follows: hydrophilic parts join together in the water layer and all lipophilic parts pass to the hydrophobic ionic liquid layer. Possibility of cation to leave the ionic liquid phase depends of the molar ratio of counter-ions in water layer and can be regulated. The key of this process is simple to explain – ionic liquid made of hydrophilic and lipophilic parts when added to aqueous/IL system will change its hydrophobic parts to more hydrophilic from ionic liquid layer.

Two CILs were prepared using this method: **$[bmim]_2$-[(*R,R*)-Trtr]** and **$[omim]_2$-[(*R,R*)-Trtr]** (Figure 4-30). The second one was not described in the literature before. Compound **$[bmim]_2$-[(*R,R*)-Trtr]** was prepared before using ion-exchange resin to prepare [bmim]OH which was introduced to the reaction with the tartaric acid[89].

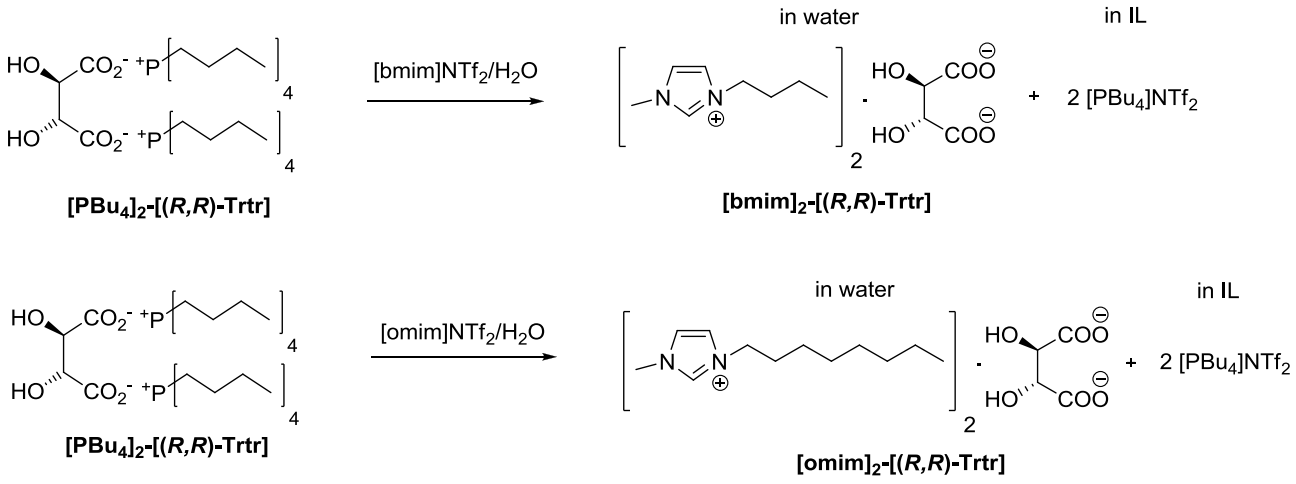


*Figure 4-30. Cross-metathesis of **$[PBu_4]_2$-[(R,R)-Trtr]** with [bmim]NTf_2 and with [omim]NTf_2.*

The second IL formed is **[PBu$_4$]NTf$_2$**, which consists of two hydrophobic parts, and it stays in IL phase. Because of its paraffin-like structure, it forms single ball when stirred (Figure 4-31).

*Figure 4-31. Ionic liquid **[PBu$_4$]NTf$_2$** forms the ball during stirring.*

Interesting to note that tartaric acid prefers omim cation to tetrabutylphosphonium because **[omim]$_2$-[(*R,R*)-Trtr]** was obtained in 100% yield in water solution. This reaction is not complete when imidazolium IL is taken in equimolar quantity so there is no second phase to partition hydrophobic molecules. It needs the presence of two immiscible phases (excess of hydrophobic IL or any hydrophobic solvent able to dissolve the reaction products) to be quantitative. Hemi-tartrate **T(*R,R*)-P$_4$** (Figure 4-24) does not proceed quantitative exchange with imidazolium ionic liquids forming compounds with fractional stoichiometry.

This very simple process gives us the way to simple synthesis of new ILs. The attraction of this method is that we are introducing to the reaction two ILs to obtain two new ILs in quantitative yield and with 100% atoms economy.

We were inspired by this reaction to make ELLE process because this reaction can be classified as ion-exchange extraction. But at first it was necessary to modify our racemic substrates to make them usable in this kind of process.

4.7.1 Modification of substrates to use in cross-metathesis

Racemic substrates were modified in order to obtain salts containing a hydrophobic part. As tartaric acid represents the negatively charged core of CIL, we can expect the interaction between the carboxylic functions of tartaric acid with amine functions of our racemic substrates. To make amine positively charged it was necessary to add an anion. This anion must be hydrophobic because it was expected to stay in the hydrophobic phase. Also, it was decided to use the same counter-ion that of commercial hydrophobic ionic liquid to limit the number of possible ionic interactions.

In our example, racemic substrates were reacted with bis(trifluoromethanesulfonyl)imide $HNTf_2$ to give bis(trifluoromethanesulfonyl)imides. Three compounds were prepared by this way: **[HPro]NTf_2**, **[HPip]NTf_2** and **[HPipeco]NTf_2** (Figure 4-32). Commercial hydrophobic ionic liquid containing NTf_2 counter-ion was chosen to dissolve all of them.

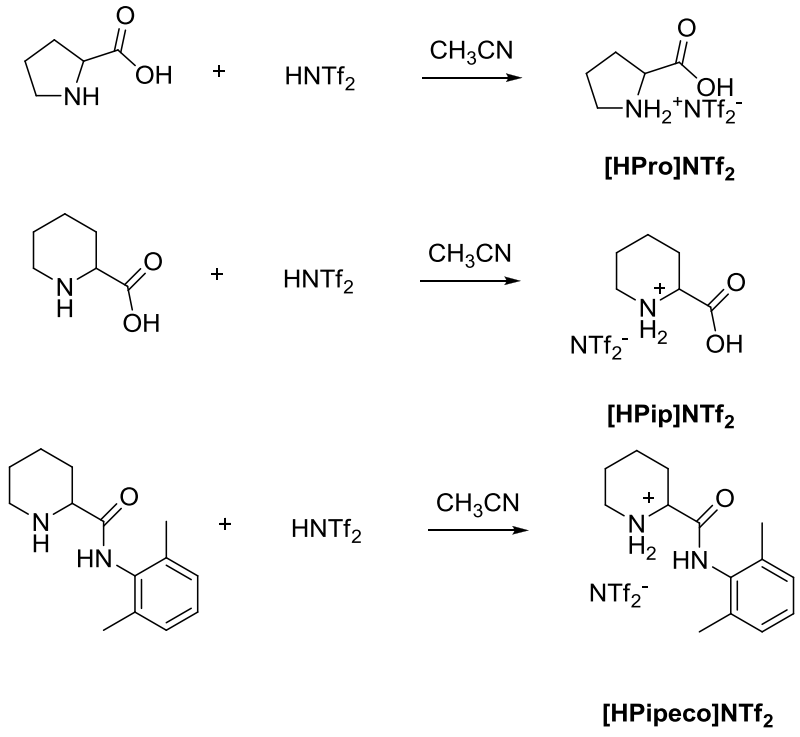


Figure 4-32. Modification of racemic substrates to use them in cross-metathesis ELLE.

Compounds **[HPip]NTf_2** and **[HPipeco]NTf_2** were not before described. Silaproline **Sip** was impossible to modify by this way because it was delivered as its trifluoroacetate and when introduced to the metathesis reaction with $LiNTf_2$ stays in water layer along with LiTFA and it is not possible to extract the desired [HSip]NTf_2 from its aqueous solution.

4.7.2 Screening of modified substrates with tetrabutylphosphonium tartrates

The biphasic chiral extraction system was established the same way as previously described (Figure 4-29) with the goal to check ELLE using discovered ion-exchange process. It was used ½ or ¼ equivalent of CILs **[PBu_4]-[(*R,R*)-Trtr]** and **[PBu_4]$_2$-[(*R,R*)-Trtr]** to 5 equivalents of commercial hydrophobic ionic liquid [omim]NTf_2. To the IL phase was added 1 equivalent of racemic compound to be resolved **[HPro]NTf_2**, **[HPip]NTf_2** or **[HPipeco]NTf_2** (Figure 4-32) and the system was mixed for 3 hours at normal conditions. 20 equivalents of water were then added and this biphasic system was stirred for 12 hours with the goal to make the preferential ion exchange of one of enantiomers. Water layer was separated, evaporated and dried under vacuum line. Figure 4-33 illustrates this process on the example of compounds **[HPro]NTf_2** and ¼ equivalent of **[PBu_4]-[(*R,R*)-Trtr]**.

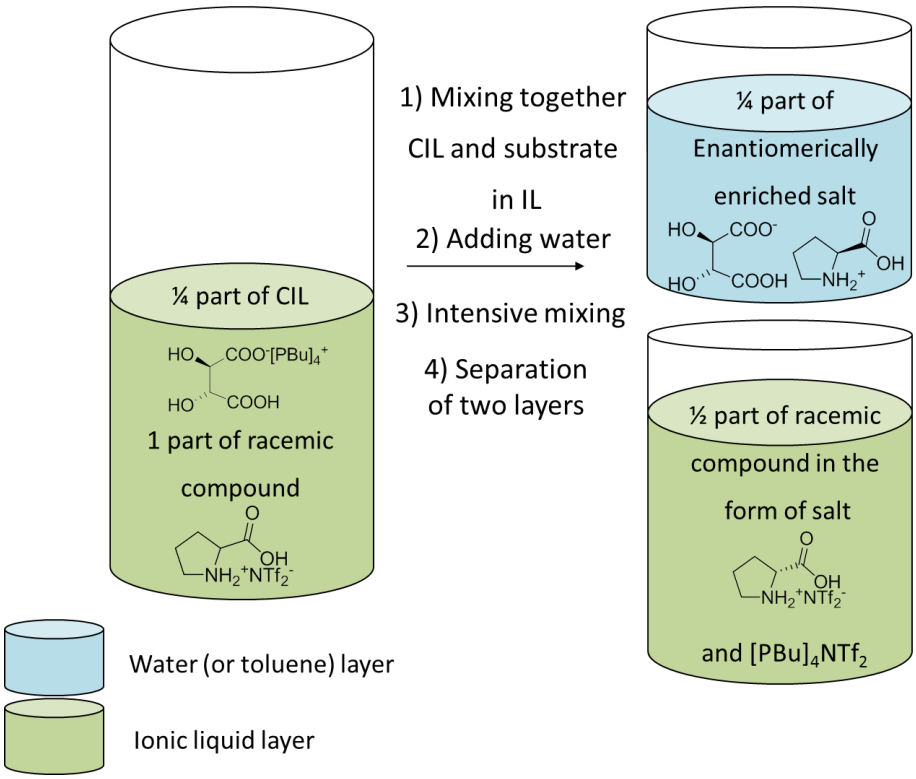


Figure 4-33. Schematic representation of one example of ELLE using cross-metathesis with chiral ionic liquids.

Totally 12 possible combinations were checked (3 racemic substrates and 2 CILs used in quantity of ½ or ¼ equivalents). Each extracted residue was analyzed by the previously described schema. The obtained results were surprisingly encouraging (Table 4-6).

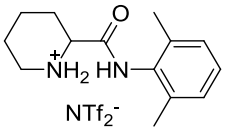
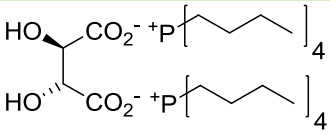
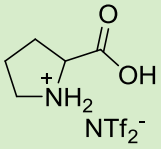
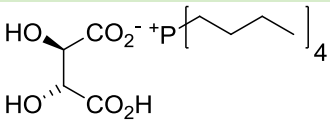
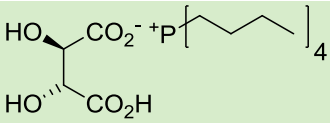
CIL	Conditions	% of initial mass	% in extracted mixture	ee	α_{op}
Racemic substrate to be resolved [HPipeco]NTf_2 1 eq. 					
 **[PBu_4]$_2$-[(*R,R*)-Trtr] 0.25 eq.**	[omim]NTf_2 5 eq.; Mixing 3h; RT; Water, 20 eq.; Extraction 12h.	10	67	**7%**	**1.15**
Racemic substrate to be resolved [HPro]NTf_2 1 eq. 					
 **[PBu_4]-[(*R,R*)-Trtr] 0.5 eq.**	[omim]NTf_2 3.36 eq.; Mixing 3h; RT; Water, 22.2 eq.; Extraction 12h.	85	63	**6%**	**1.80**
 **[PBu_4]-[(*R,R*)-Trtr] 0.25 eq.**	[omim]NTf_2 3.36 eq.; Mixing 3h; RT; Water, 22.2 eq.; Extraction 12h.	65	55	**7%**	**1.47**

Table 4-6. Results of first chiral ion cross metathesis using chiral ionic liquids.

Enantiomerically enriched substrates were extracted as their tartrates. No other substances were determined in the extracted mixture. Maximal value of ee was 7% and operational selectivity α_{op} vary from 1.09 up to 1.80. As mentioned before, a minimal selectivity of 1.5 is necessary to avoid the excessive number of fractional extraction steps. Therefore, we can assume that the chiral extraction using cross-metathesis (ion exchange) with CILs has stronger separation ability as perspective industrial method of ELLE. But numerous factors affecting the extraction efficiency need to be more precisely analyzed, namely the influence of the concentrations of the host and substrate, the types of the used ILs, mixing method and time to reach equilibrium, temperature, etc.

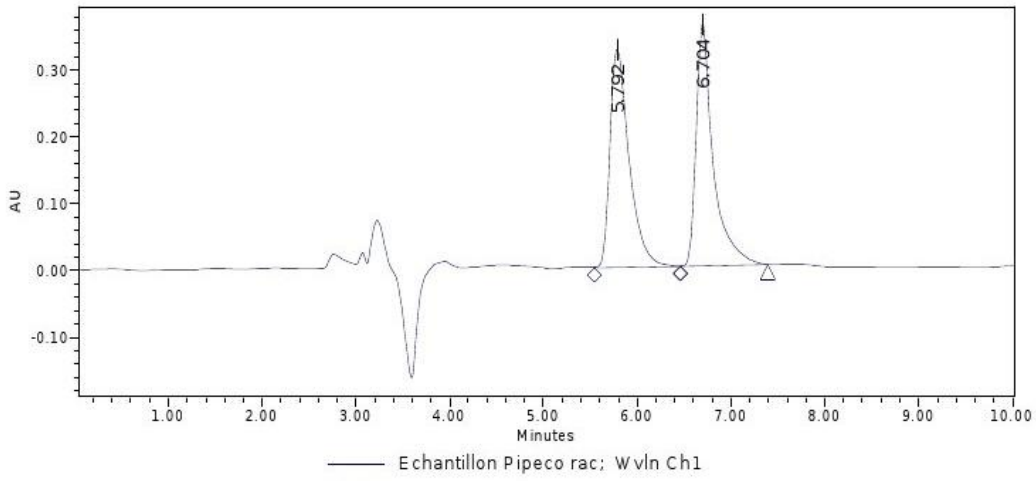
4.8 Study of important parameters for one chosen system

To improve the enantiomeric excess of chosen ELLE process, it is important to know the role of factors influencing chiral recognition. They include concentration and the role of co-solvent IL, host/substrate ratio, temperature, etc. We preferred to choose only one extraction to study precisely influencing factors with the goal to work out it increasing ee and α_{op}.

As racemic substrate chosen was the pipecoloxylidide **Pipeco,** despite higher ees for proline derivatives. As chiral hosts, two tetrabutylphosphonium tartrates **[PBu_4]-[(*R,R*)-Trtr]** and **[PBu_4]$_2$-[(*R,R*)-Trtr]** were chosen. The preference for the pipecoloxylidide was given because of some reasons. First and the main one, because it was one of the model compounds of the INTENANT project. Second, due to its structure, it is visible in UV, making the correct detection of small differences in ee possible. CILs tetrabutylphosphonium tartrates were chosen because of their simple and inexpensive preparation way.

For the moment, in the industrial process, useful (*S*)-enantiomer was obtained through the diastereomeric salt resolution with *O,O*-dibenzoyl *L*-tartaric acid leaving the (*R*)-enantiomer as waste. But in the frame of the INTENANT project a method for the racemization of pipecoloxylidide using a ruthenium catalyst was developed in 2010 [114]. This racemization method can be combined in an integrated process that combines the separation of two enantiomers by ELLE in ILs with racemization of the undesired enantiomer.

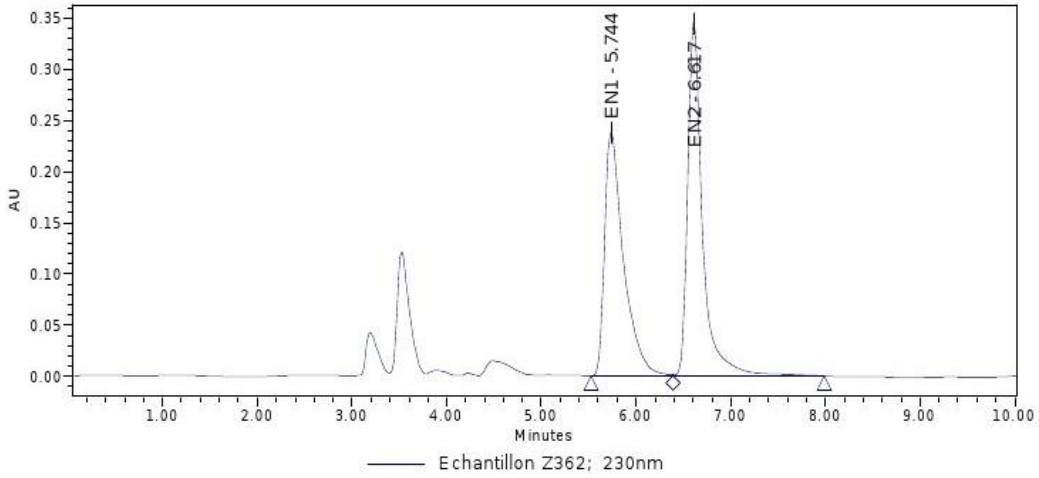
Finally, cross-metathesis process was chosen because of its ion-exchanging nature, working more efficiently in many cases as complexation mechanism what is known from the literature (see part 3.9). Examples of two HPLC chromatograms of the racemic pipecoloxylidide (Figure 4-34) and one of ELLEs chosen for advanced study are presented on Figure 4-35 (here and below: peaks at 3-4 minutes are the column artifacts of injection; peak 5.7 min is **Pipeco** distomer (*R*), peak 6.7 min is eutomer (*S*)). It is important to notice that natural tartaric acid (*R,R*) extracts to water layer enantiomer of interest: (*S*)-**Pipeco**.



Résultats d'intégration

	RT	Name	Height	Area	% Area	Int Type	Concentration	Units
1	5.792		326834	4660532	50.35	VV		
2	6.704		363252	4595745	49.65	Vb		

Figure 4-34. HPLC chromatogram of the racemic pipecoloxylidide



Résultats d'intégration

	RT	Name	Height	Area	% Area	Int Type	Concentration	Units
1	5.744	EN1	238227	3310867	46.66	BV		
2	6.617	EN2	346191	3785115	53.34	VB		

Figure 4-35. HPLC chromatogram of the chosen ELLE to study.

First parameter to check was the role of co-solvent IL. Two extractions were performed without [omim]NTf_2 between 1 eq. of pipecoloxylidide and 0.5 equivalent of tetrabutylphosphonium tartrates **[PBu_4]-[(*R,R*)-Trtr]** and **[PBu_4]$_2$-[(*R,R*)-Trtr]**. Extraction media was stirred for 12 hours with 100 equivalents of water to yield zero % ee. Interesting to note that in the case of **[PBu_4]-[(*R,R*)-Trtr]** another pure salt was extracted: **[HPipeco]-[(*R,R*)-Trtr]** (Figure 4-36).

To confirm the importance of co-solvent IL for ELLE, previous extractions were repeated without co-solvent IL and only with 0.25; 0.5; 0.75; 1 and 2 equivalents of tetrabutylphosphonium tartrates **[PBu$_4$]-[(*R,R*)-Trtr]** and **[PBu$_4$]$_2$-[(*R,R*)-Trtr]** respectively (10 extractions in total). No ee was observed in all examples. This observation confirms the important role of co-solvent IL for the efficiency of ELLEs. This can be explained by the increasing of stability of ion pair host/substrate by putting them into IL media and by lowering down the speed of exchange between ion pairs.

Anyway, cross-metathesis works perfectly leading to tartaric acid to extract the pipecoloxylidide in the form of the tartrates **[HPipeco]-[(*R,R*)-Trtr]** and **[HPipeco]$_2$-[(*R,R*)-Trtr]**. Hemi-tartrate **[PBu$_4$]-[(*R,R*)-Trtr]** extracted pure **[HPipeco]-[(*R,R*)-Trtr]** when tartrate was added in the quantity up to 0.75 equivalents. Compound **[PBu$_4$]$_2$-[(*R,R*)-Trtr]** makes possible to extract pure **[HPipeco]$_2$-[(*R,R*)-Trtr]** only when its ratio do not exceed 0.25 equivalent. When tetrabutylphosphonium tartrates were more concentrated that mentioned above ratios, tartrates with fractional stoichiometry were extracted.

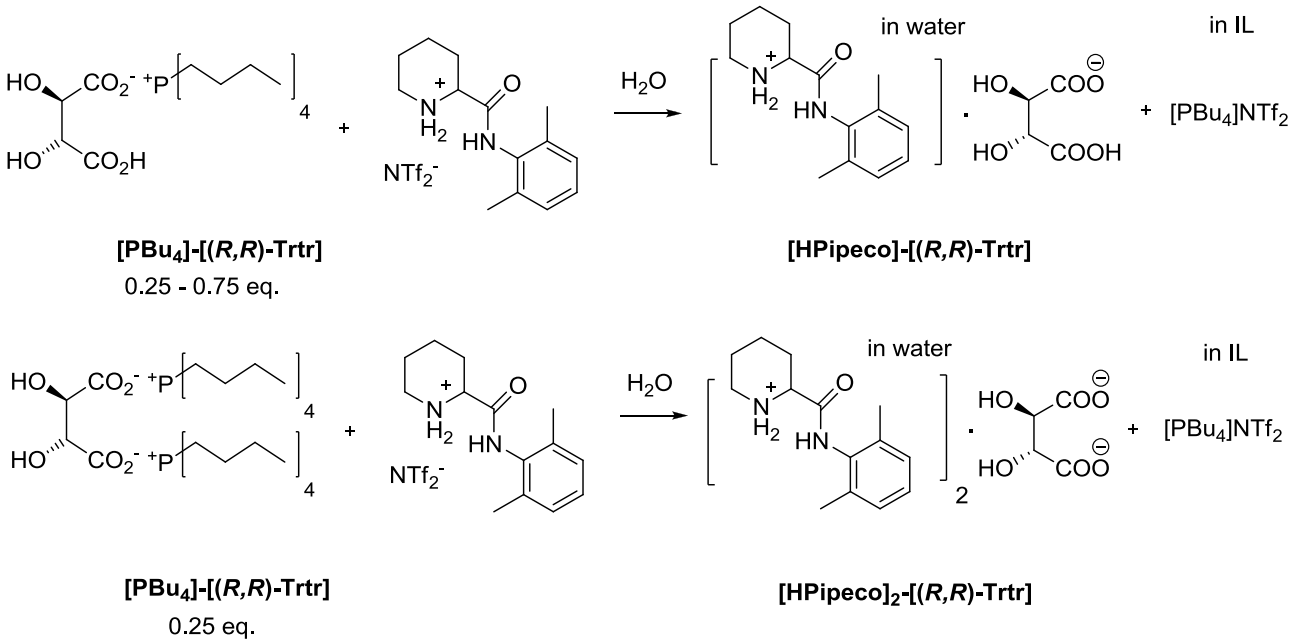


Figure 4-36. Formation of pipecoloxylidide tartrates using cross-metathesis.

Next parameter to check was to determine the minimal quantity of co-solvent IL [omim]NTf$_2$ when our extractions still produce enantiomeric excess. In 7 different tests, one equivalent of **[HPipeco]NTf$_2$** was mixed with 0.25; 0.5; 0.75; 1; 2; 4 and 5 equivalents of [omim]NTf$_2$ respectively. After 3 hours of mixing, every solution was extracted by 20 eq. of water.

In the range from 0.25 to 0.75 eq. of [omim]NTf_2 no ee was observed. From 1 to 4 eq. [omim]NTf_2 values of ee about 4% were observed. Only small improvement of 1% ee was observed when using 4 equivalents of [omim]NTf_2 (Table 4-7).

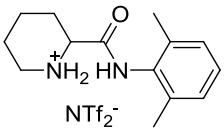
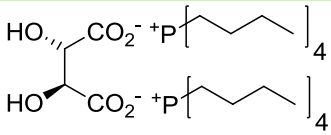
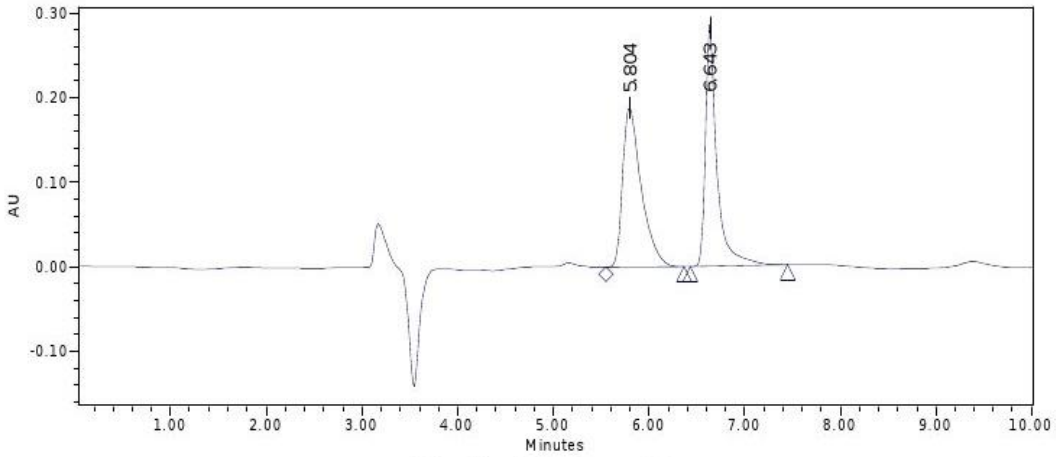
Racemic substrate to be resolved [HPipeco]NTf_2 1 eq. 					
CIL	Conditions	% of initial mass	% in extracted mixture	**ee**	**α_{op}**
 **[PBu_4]$_2$-[(*S,S*)-Trtr] 0.25 eq.**	[omim]NTf_2 **1 eq.**; Mixing 3h; RT; Water, 20 eq.; Extraction 12h.	20	65	**4%**	**1.10**
	[omim]NTf_2 **2 eq.**; Mixing 3h; RT; Water, 20 eq.; Extraction 12h.	8	64	**4%**	**1.09**
	[omim]NTf_2 **3 eq.**; Mixing 3h; RT; Water, 20 eq.; Extraction 12h.	7	63	**4%**	**1.09**
	[omim]NTf_2 **4 eq.**; Mixing 3h; RT; Water, 20 eq.; Extraction 12h.	10	67	**5%**	**1.11**

Table 4-7. Results of the study of co-solvent effect.

Also, in this series (*S,S*)-enantiomer of tartrate was used to check the possibility to invert the discrimination order of **Pipeco**. As it was expected, the inversion of preferentially extracted enantiomer was observed (to compare the Figure 4-37 with the Figure 4-35).



Résultats d'intégration

	RT	Name	Height	Area	% Area	Int Type	Concentration	Units
1	5.804		188765	2565237	52.01	VB		
2	6.643		283561	2367420	47.99	BB		

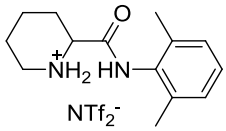
Figure 4-37. Inversion of preferentially extracted enantiomer by changing enantiomer of CIL.

To eliminate the version of possible influence of [omim]NTf_2 on ee, the next experiment was done. Ionic liquid [omim]NTf_2 was changed to [b2,3mim]NTf_2 (1-Butyl-2,3-dimethylimidazolium bis(trifluoromethanesulfonyl)imide). The last one in amount of 5 equivalents was mixed with 1 equivalent of **[HPipeco]NTf_2** and 0.25 equivalent of **[PBu_4]$_2$-[(*R,R*)-Trtr]** and mixed for 2 hours. After 12h of extraction with 20 equivalents of water 2% of ee was determined.

Another checked parameter was the effect of temperature. In 8 different tests, one equivalent of **[HPipeco]NTf_2** was mixed with 5 equivalents of co-solvent IL [omim]NTf_2 and heated or cooled for 2 hours at 0; 30; 50; 80; 100; 125; 150 and 180°C respectively. Experiment performed at 0°C, was extracted at the same temperature. All others experiments were cooled to the room temperature and every solution was extracted by 20 eq. of water.

Obtained results were promising (Table 4-8). Apparently, heating increases dramatically enantiomeric excess, reaching the maximum at 50°C (Figure 4-38). Further increasing of temperature slightly decreases ee. At 150°C reaction mixture starts to turn yellow and becomes completely black at 180°C due to degradation of CIL or substrate. At 0°C no ee was observed.

Racemic substrate to be resolved [HPipeco]NTf_2 1 eq.



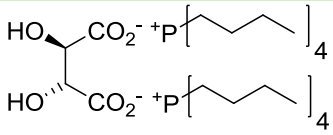
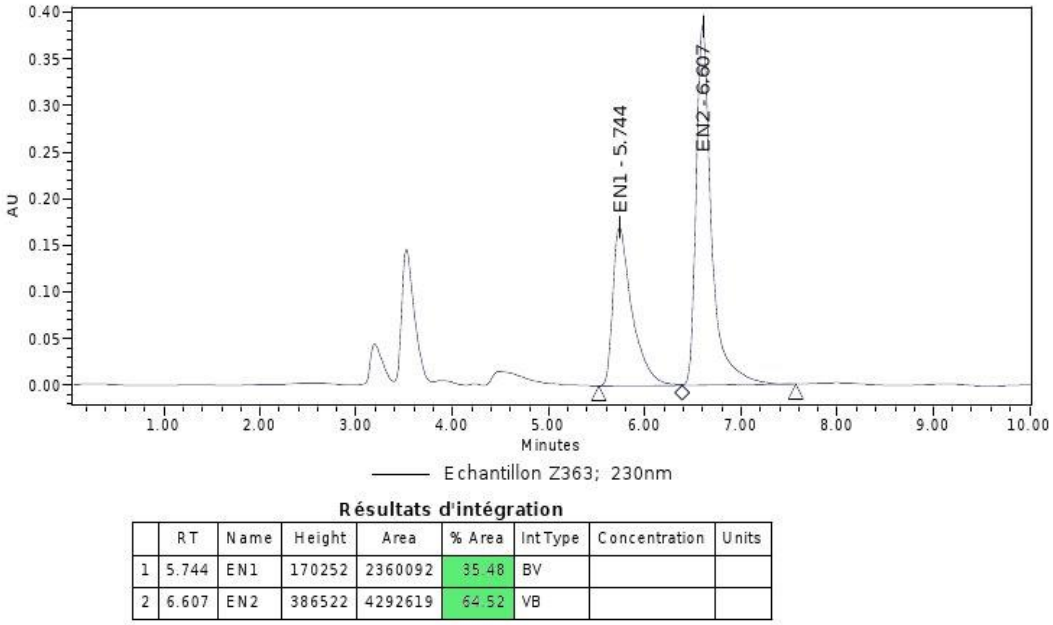
CIL	Conditions	% of initial mass	% in extracted mixture	ee	α_{op}
 **$[PBu_4]_2$-[(*R*,*R*)-Trtr] 0.25 eq.**	[omim]NTf_2 5 eq.; Mixing 2h at **30°C**; Water, 20 eq.; Extraction 12h.	10	63	**18%**	**1.47**
	[omim]NTf_2 5 eq.; Mixing 2h at **50°C**; Water, 20 eq.; Extraction 12h.	9	63	**30%**	**1.97**
	[omim]NTf_2 5 eq.; Mixing 2h at **80°C**; Water, 20 eq.; Extraction 12h.	8	63	**8%**	**1.21**
	[omim]NTf_2 5 eq.; Mixing 2h at **100°C**; Water, 20 eq.; Extraction 12h.	1.3	40	**14%**	**1.33**
	[omim]NTf_2 5 eq.; Mixing 2h at **125°C**; Water, 20 eq.; Extraction 12h.	7	63	**26%**	**1.75**
	[omim]NTf_2 5 eq.; Mixing 2h at **150°C**; Water, 20 eq.; Extraction 12h.	1.3	40	**22%**	**1.57**
	[omim]NTf_2 5 eq.; Mixing 2h at **180°C**; Water, 20 eq.; Extraction 12h.	16%	62%	**4%**	**1.08**

Table 4-8. Results of the study of temperature effect.



Résultats d'intégration

	RT	Name	Height	Area	% Area	Int Type	Concentration	Units
1	5.744	EN1	170252	2360092	35.48	BV		
2	6.607	EN2	386522	4292619	64.52	VB		

Figure 4-38. The best example of ELLE showing ee = 30% after 2h at 50°C.

The relationship between enantiomeric excess and temperature is presented on Figure 4-39. Enantiomeric excess starts from zero at 0°C and quickly rises up to 30 % at 50°C. This can be explained by reaching the activation energy of formation of intermolecular complexes between CIL and one enantiomer of the racemic substrate. Then, ee starts to decrease progressively to reach almost zero at 180°C, along with decomposition of starting material. Progressive decrease of ee can be explained by thermodynamic processes resulting in destruction of diastereomeric complexes. Some experiments showed deviations from the baseline thus indicating that this preliminary explanation needs to be confirmed by the solid study of mechanism of the enantioselective recognition.

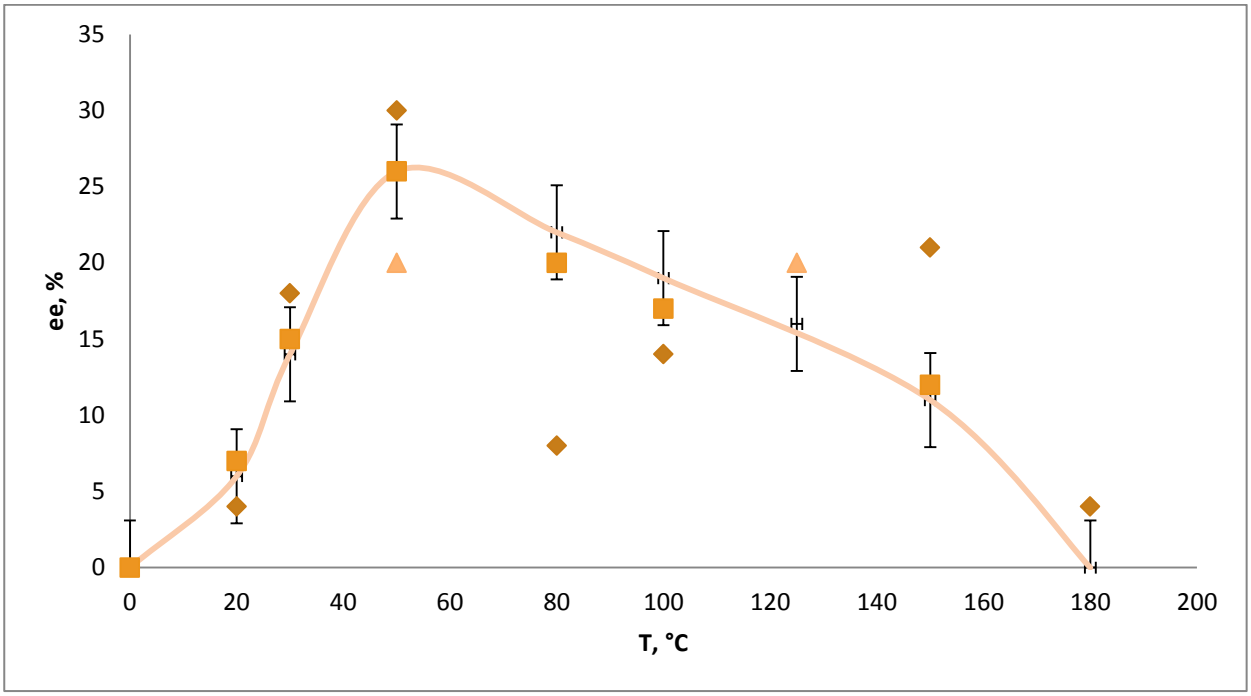


Figure 4-39. Relationship between ee and T. Different shape of points represents different runs.

To prove that observed effect of increasing ee with temperature is not related to deracemization of our racemic substrate in the chiral medium, the next experiment was performed. The mixture of 5 equivalents of **$[PBu_4]_2$-[(*R,R*)-Trtr]** was mixed with 1 equivalent of pipecoloxylidide and permitted to interact for 2 days at 50°C. No enantiomeric enrichment was observed.

To check the version of possible role of temperature on **$[PBu_4]_2$-[(*R,R*)-Trtr]**, it was heated at 150°C for 2 hours with 5 equivalents of [omim]NTf_2, and after cooling to RT, **[HPipeco]NTf_2** and water were then added. After 12h of extraction with 20 equivalents of water, no ee was observed. This observation proves the importance of incubation time between tartrate CIL and **[HPipeco]NTf_2**.

The role of traces of water during incubation period was checked. For this purpose starting CIL **$[PBu_4]_2$-[(*R,R*)-Trtr]** was dried during 3 days in exsiccator in the presence of P_2O_5. Then, it was heated at 50°C for 2 hours with **[HPipeco]NTf_2** in 5 equivalents of [omim]NTf_2 and extracted as previously described. Almost the same ee was observed comparing with ELLE with non-dried **$[PBu_4]_2$-[(*R,R*)-Trtr]** : 26% to 30%. This proves that traces of water do not influence dramatically the ee.

The best example of ELLE (ee= 26-30%) was tested with another enantiomer of tartrate: **$[PBu_4]_2$-[(*S,S*)-Trtr]** instead of **$[PBu_4]_2$-[(*R,R*)-Trtr].** It was heated at 50°C for 2 hours with

[HPipeco]NTf$_2$ in 5 equivalents of [omim]NTf$_2$ and extracted by water. Enantiomeric excess of 20% was determined along with inversion of extracted to water enantiomer: **(*S,S*)-Tartrate** extracts **(*R*)-Pipeco**.

The possibility to extract several times the same raffinate was checked. **[PBu$_4$]$_2$-[(*R,R*)-Trtr]**, it was heated at 150°C for 2 hours with **[HPipeco]NTf$_2$** in 5 equivalents of [omim]NTf$_2$. After cooling to the RT, 20 equivalents of water were added and extracted for 12h. Extraction by water was repeated 3 times. The results are presented in Table 4-9 and show good efficiency of second extraction which decreases when extracted at third time.

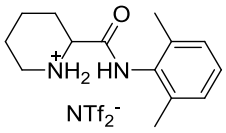
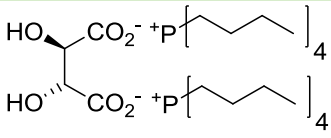
Racemic substrate to be resolved [HPipeco]NTf$_2$ 1 eq. 					
CIL	Conditions	% of initial mass	% in extracted mixture	**ee**	**α_{op}**
 **[PBu$_4$]$_2$-[(*R,R*)-Trtr] 0.25 eq.**	[omim]NTf$_2$ 5 eq.; Mixing 2h at **150°C**; 1st extraction: Water, 20 eq.; Extraction 12h.	1.3	40	**22%**	**1.57**
	2nd extraction: Water, 20 eq.; Extraction 12h.	4	62	**14%**	**1.34**
	3rd extraction: Water, 20 eq.; Extraction 12h.	3	60	**4%**	**1.08**

Table 4-9. Multiple extractions of one raffinate.

All gathered data permit us to conclude that all observed enantiomeric excesses are related to the enantioselective liquid-liquid extraction using chiral ionic liquids as resolving hosts. Presented here examples are the very first data of ELLE in CILs, which needs to be extended by studying the mechanism of interactions, scaling effect, recycling of ILs and the breadth of selectivity towards other racemic substrates.

Our best example shows an enantiomeric excess of 30% and operational selectivity 1.97. This is the first example of metal-free ELLE in ionic liquids and this is the promising technique in the field of preparation of enantiomerically pure compounds.

5 Conclusion

Le but de cette recherche a été de vérifier la possibilité de l'extraction liquide-liquide énantiosélective par les liquides ioniques chiraux. Ce travail a démontré que cette idée est très prometteuse pour la préparation de composés énantiomériquement purs. Le meilleur exemple montre un excès énantiomérique de 30% et une sélectivité opérationnelle de 1,97. C'est le premier exemple d'ELLE utilisant les liquides ioniques chiraux et sans usage d'ions métalliques.

Nous avons choisi un système d'ELLE pour étudier précisément les facteurs influant sur l'ee et la sélectivité opérationnelle α_{op}. Plusieurs paramètres pour ce système choisi ont été étudiés, tels que la concentration et le rôle du IL co-solvant, le rapport hôte/substrat, la température, etc. Nous avons montré que la température est le facteur le plus influent sur la reconnaissance chirale par rapport aux autres paramètres. Le liquide ionique co-solvant est très important pour l'observation d'un ee. L'excès énantiomérique commence à apparaitre à partir du rapport équimolaire de LIC/LI, et l'augmentation postérieure du LI co-solvant n'augmente plus l'ee.

Comme hôtes chiraux pour ELLE, nous avons choisi d'utiliser les liquides ioniques chiraux. Dans ce travail, nous renouvellons la conception de la synthèse de nouveaux sélecteurs chiraux utiles pour les processus de dédoublement en phase liquide. Trois familles de liquides ioniques chiraux ont été développées (Figure 5-1). Une famille est complètement nouvelle et basée sur le 1,2-diaminocyclohexane. Pour toutes les familles, les conditions de synthèse et de purification ont été développées et améliorées. Dans tous les cas, nous avons choisi des méthodes de synthèse donnant accès à des quantités importantes de composés, au moins à l'échelle de plusieurs grammes.

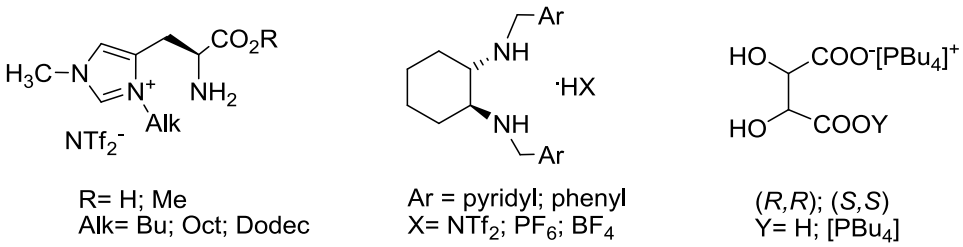


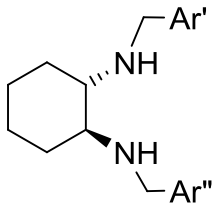
Figure 5-1. Trois familles développées de liquides ioniques chiraux.

Pour la synthèse des histidiniums LIC nous avons utilisé la (*S*)-histidine, un acide aminé naturel. Sa structure particulière, contenant un imidazole nous a permis de faire la dissymétrisation par

alkylation du noyau imidazole de la chaîne latérale, laissant libre la fonction acide aminé dans les liquides ioniques chiraux obtenus.

Nous avons modifié la synthèse existante des LIC histidiniums pour faire la déprotection de fonctions acides aminés et la métathèse «one pot». Les LIC histidiniums ont été précipités presque quantitativement en ajustant le pH de la solution à la neutralité. Cette méthode a été testée sur une quantité multigramme et a montré de bons résultats. La précipitation sélective peut être utilisée comme méthode de purification appropriée pour les liquides ioniques hydrophobes contenant une partie acide aminé.

Une partie du projet INTENANT était la synthèse de tous les produits possibles de la réaction entre le (1*S*,2*S*)-diaminocyclohexane avec les benz-, pyridine-2-, pyridine-3- et pyridine-4 carboxaldéhydes. (Table 5-1).



Composé	Ar'	Ar"	Nature
D2,Ph	Ph	2-pyridyl	*Mixte*
D3,Ph	Ph	3-pyridyl	*Mixte*
D4,Ph	Ph	4-pyridyl	*Mixte*
D2,2	2- pyridyl	2-pyridyl	*Symétrique*
D3,3	3- pyridyl	3-pyridyl	*Symétrique*
D4,4	4- pyridyl	4-pyridyl	*Symétrique*
D3,2	2- pyridyl	3-pyridyl	*Dissymétrique*
D4,2	2- pyridyl	4-pyridyl	*Dissymétrique*
D4,3	3- pyridyl	4-pyridyl	*Dissymétrique*

Table 5-1. Les dérivés de DACH.

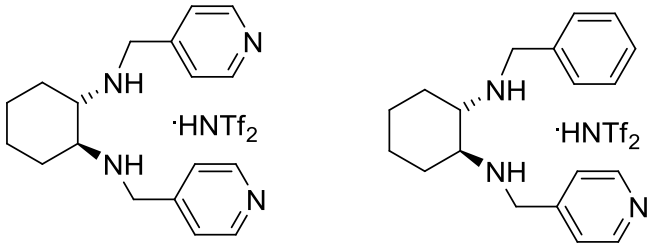
Nous nous sommes engagés sur la synthèse des neuf cibles possibles: trois composés sont mixtes (portant à la fois le phényle et le résidu pyridyl), trois sont symétriques (portant deux résidus pyridyl identiques) et trois autres sont dissymétriques (portant deux résidus différents pyridyl). Au début de ce projet en 2008, seulement deux composés de cette série étaient connus, **D2,2** et **D4,Ph**. En 2009 la synthèse des composés **D3,3** et **D4,4** a été publiée (voir la

partie 3.5). Enfin, cette étude représente les premières données complètes pour l'ensemble des composés.

Les composés basés sur le 1,2-diaminocyclohexane que nous avons synthétisés ont été planifiés pour servir à deux buts. Tout d'abord, pour les fournir à l'équipe WP4 "Cristallisation" d'INTENANT pour les tests d'auto-cristallisation préférentielle ensemencée. En tout, huit diamines chirales et deux racémiques en quantité de 2 g chacune ont été transmises à l'Université de Rouen pour les applications dans la cristallisation préférentielle.

Le deuxième objectif de préparation des composés basés sur le 1,2-diaminocyclohexane était le développement d'une nouvelle classe de liquides ioniques chiraux. Un grand nombre de tentatives d'alkylation de ces composés a été effectué sans succès. Enfin, il a été démontré qu'il n'y a pas de moyen simple d'accéder aux pyridines alkylées contenant la fonction amine secondaire dans la structure de la molécule. Une autre voie doit être proposée pour créer le produit souhaité alkylé.

Enfin, malgré les échecs de l'alkylation, nous avons réussi l'accès à une nouvelle famille de liquides ioniques à température ambiante chiraux (Figure 5-2). Le composé **D4,Ph-HNTf$_2$** a une température de transition vitreuse de +0,3°C, et son analogue structural **D4,4-HNTf$_2$** a une température de transition vitreuse de +5,1°C.



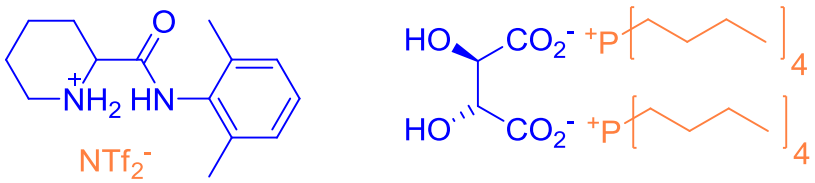
D4,4-HNTf$_2$ **D4,Ph-HNTf$_2$**

Figure 5-2. Deux composés de la nouvelle famille des liquides ioniques à température ambiante chiraux "chiral ionic liquid benzathines" (CILBs).

La synthèse du LIC effectuée à partir de l'acide tartrique et de l'hydroxyde de tétrabutylphosphonium est assez simple et consiste uniquement à mélanger deux solutions aqueuses de composés disponibles commercialement. Malgré la simplicité de cette méthode, une grande attention doit être portée sur la pureté des composés de départ. Notre découverte des problèmes de détermination de la pureté des LIs reçus révèle l'importance de faire attention lors de l'utilisation des données de recherches antérieures.

La métathèse croisée est peut-être la découverte la plus intéressante de ce travail. Simple et puissant ce procédé ouvre la voie à la synthèse simple des nouveaux liquides ioniques. Chaque liquide ionique de départ doit possèder une partie hydrophile et une partie hydrophobe. Ensemble dans le système biphasique, les ions se répartissent selon leur nature. L'avantage de cette méthode est que nous mettons en réaction deux liquides ioniques pour obtenir deux nouveaux liquides ioniques avec un rendement quantitatif et avec 100% d'économie d'atomes.

Nous avons été inspirés par cette réaction de métathèse croisée pour développer le processus d'ELLE dans les LIs. Tous les composés racémiques ont été modifiés en ajoutant un anion hydrophobe dans leurs structures pour les rendre utilisables dans ce genre de processus. Les LIC tartrates de tétrabutylphosphonium ont été choisis en raison de leur simple mode de préparation. Le composé racémique que nous avons sélectionné pour les tests approfondis était le pipécoloxylidide, parce qu'il a été le substrat modèle du projet INTENANT. Finalement, la paire LIC tartrate/ pipécoloxylidide a donné les meilleurs résultats de ce travail (Figure 5-3).



[HPipeco]NTf$_2$ **[PBu$_4$]$_2$-[(*R*,*R*)-Trtr]**

Figure 5-3. La paire tartrate de tétrabutylphosphonium / pipécoloxylidide qui a donné les meilleurs résultats d'ELLE. Les ions bleus sont hydrophiles et les ions oranges sont hydrophobes.

Dans le cadre du projet INTENANT, une méthode de racémisation du pipécoloxylidide utilisant un catalyseur de ruthénium a été élaborée[114]. Cette méthode pourra être intégrée dans un processus qui va combiner la séparation des deux énantiomères par ELLE en LIC avec racémisation de l'énantiomère non désiré.

Les perspectives de ce travail sont nombreuses. Elles concernent:

- l'étude plus approfondie des paramètres du système d'ELLE dans des LIs responsables de l'excès énantiomérique et la sélectivité opérationnelle α_{op}
- l'étude du mécanisme d'ELLE dans LIs et sa physico-chimie
- l'étude d'ELLE avec d'autres liquides ioniques chiraux et d'autres substrats racémiques différents

- le développement d'un modèle qui va permettre de choisir la structure du liquide ionique chiral pour résoudre un composé racémique précis

Pour le succès de futures études d'ELLE avec les LIC il est conseillé de:

- choisir des substrats racémiques pour lesquels les faibles valeurs d'ee peuvent être facilement déterminées avec les méthodes «express» (donc pour HPLC chirale, ils doivent contenir des chromophores)
- choisir des liquides ioniques chiraux facilement accessibles en grand quantité
- vérifier la stœchiométrie de tous les liquides ioniques par l'analyse élémentaire

Le but du projet INTENANT consistait à améliorer la production des énantiomères purs par combinaison intelligente de la séparation (chromatographie, cristallisation...) et de la réaction (synthèse, racémisation...).

Les résultats du projet INTENANT sont très avantageux. Les partenaires industriels ont obtenu:

- les protocoles de validation pour étudier et pour caractériser le comportement d'un système chiral d'intérêt dans le contexte du procédé
- les connaissances sur les avantages et les inconvénients des approches «chirales» *vs* des approches «racémiques»
- les approches novatrices dans les domaines de la synthèse, de la chromatographie, de la cristallisation, et de la racémisation
- les modèles quantitatifs simplifiés pour les procédés et des combinaisons de processus basés sur des modèles simples
- les nouveaux systèmes de processus validés
- les logiciels pour l'optimisation de procédés
- le programme de formation des personnels

Les avantages acquis pour les partenaires académiques ont été les suivants:

- la meilleure compréhension de concepts énantiosélectifs et non sélectifs de la synthèse
- la compréhension améliorée d'outils généraux de la racémisation, soit chimique soit par la catalyse enzymatique

- la meilleure compréhension de la thermodynamique et de la cinétique de la cristallisation et de la chromatographie
- la disponibilité de large quantité de données concernant les exemples étudiés
- la mise en place de méthodes pour raccourcir et optimiser des procédés complexes

A ce jour, 35 publications ont été déjà soumises. La liste de tous les travaux est disponible sur le site d'INTENANT[115]. Une issue spéciale du journal «Organic Process Research & Development» est prévue, dans lequel notre article a été déjà accepté[116].

Cinq cours pour les participants du projet ont été donnés: sur la cristallisation, la synthèse biologique, la synthèse organique, la chromatographie préparative et l'optimisation de procédés. Le matériel de ces cours a donné la base pour le «Training Package», qui pourra être utilisé pour la formation de personnels.

L'expérience du projet INTENANT a changé l'approche des industriels vers le design de procédé: «*Ce qui était assez bien pour des projets, n'est plus assez bien maintenant!*» (AstraZeneca).

6 Experimental part

6.1 General information

General considerations

The following solvents and reagents were dried prior to use: CH_2Cl_2, Et_2O, THF, MeOH, Et_3N (from calcium hydride, stored over potassium hydroxide pellets). Benzaldehyde, pyridine-2-carboxaldehyde, pyridine-3-carboxaldehyde, pyridine-4-carboxaldehyde, benzylamine were distilled before use.

EtOH, petroleum ether, toluene and other starting materials were obtained from commercial suppliers or prepared according to literature procedures.

We thank to: Professor G. Coquerel from Université de Rouen for generous gift of racemic sample of 1,2-diaminocyclohexane; Doctor M. Hedberg from AstraZeneca for generous gifts of racemic sample of pipecoloxolydide and enantiopure (*S,S*)-1,2-cyclohexanediamine; Doctor Florine Cavelier from Institut des Biomolécules Max Mousseron for generous gifts of racemic and enantiopure samples of silaproline.

Chromatography

Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60F254 precoated plates. Chromatograms were observed under UV light and/or were visualised by heating plates that were dipped in 10 % phosphomolybdic acid in ethanol or Dragendorff reagent. Column chromatographies were carried out with SDS 35-70 µm flash silica gel or Aluminium oxide 90 active basic 0.063-0.200 mm from Merck.

Analytical Chiral HPLC analyses were run with an Alliance Waters 2695 Separation module and UV Waters 2996 Photodiode array detector, Waters 2420 ELS detector and Quick Start Empower Software, Build 1154.

Chiral HPLC conditions for proline: Column Chirobiotic T, eluent H_2O/MeOH = 80/20, flow 1 mL/min, sample concentration 1 mg/mL, ELS detection. For pipecolinic acid: Column Chirobiotic T, eluent 65% CH_3COONH_4 5mM solution pH=5.5 and 35% CH_3CN, flow 1 mL/min, sample concentration 1 mg/mL, ELS detection. For silaproline: Column Chirobiotic T, eluent $HCOONH_4$ pH= 4/MeOH = 50/50, flow 1 mL/min, sample concentration 1 mg/mL, detection UV

210 nm. For pipecoloxylidide: Column Chiracel OJ-H, eluent Heptane/diethylamine/*i*-PrOH =90/0.1/10, flow 1 mL/min, sample concentration 1 mg/mL, detection UV 230 nm.

Optical rotation Measurement

Optical rotations were measured on a Perkin-Elmer model 241 Polarimeter for the sodium D line 589 nm at RT.

Melting points

Melting points were determined by Mettler Toledo MP50 automatic Melting Point System. Each sample is approximately 5 mg weight and is analyzed in glass capillaries. Melting points were determined at inflection point and verified using internal video record.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed using Mettler Toledo DSC1 STAR^e system. Compounds were encapsulated in 40 µL capsules and introduced to cycles -80° → +50° → -80°C with ΔT speed 10°C/min. Melting points or glass transition states were determined on temperature rising curves on half-distance of baseline change. Glass transitions were measured with relaxation when it was present.

Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopic data were obtained with Bruker Advance 300 and Bruker Advance 400. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak using tables of chemical shifts of solvents[117]. The chemical shifts are expressed in ppm. The coupling constants (*J*) are expressed in Hz. The multiplicities of the signals are abbreviated as: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), etc.

Infra-Red Spectroscopy

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrometer using CaF_2 plates.

Mass spectrometry

Mass spectrometry (MS) data were obtained on the PE Sciex API 365 and Applied Biosystems Q Trap spectrometer.

Elemental analysis

Elemental analyses are obtained from Perkin Elmer microanalyser CHNS series 2 for H, C and N elements.

Water titration

Content of water in products was measured using Mettler Toledo Karl Fisher DL32 Coulometer, suitable for samples with water content 50-1000 µg per sample.

pH

Measurement of pH was performed using WTW 315i pH/mV Pocket Meter, calibrated to 3 points using commercial standard solutions of pH 10.01, 7.00 and 4.00.

Crystal Structure Determination

To determine the structures of compounds the selected crystals were mounted on a glass fibber using perfluoropolyether oil and cooled rapidly to 193 K in a stream of cold N_2. X-ray intensity data of crystals were collected with graphite-monochromated MoK_α radiation (wavelength = 0.71073 Å) by using phi- and omega- scans on a Bruker-AXS kappa APEX II Quazar diffractometer using a 30 W air-cooled microfocus source (ImS) with focusing multilayer optics at a temperature of 193(2)K.

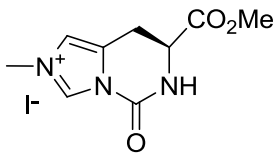
The data were integrated with SAINT, and an empirical absorption correction with SADABS was applied[118119]. The structure was solved by direct methods (SHELXS-97)[120], and refined against all data by the full-matrix least-squares methods on F^2(SHELXL-97)[121]. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their Uiso values constrained to 1.2 Ueq of their pivot atoms.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications. These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

6.2 Chiral ionic liquids based on histidinium salts

(S)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-2-methyl-5-oxoimidazo-[1,5-c]pyrimidinium iodide; H1

To a suspension of (+)-(7*S*)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidine (CAS: [69614-04-6], 2.9 g, 14.8 mmol) in acetonitrile (150 mL) was added 10 equivalents of methyl iodide. The reaction mixture was heated at 40°C overnight. The mixture was cooled, evaporated to dryness in vacuo to give pure compound as white crystals.



$C_9H_{12}IN_3O_3$

M = 337.11 g.mol^{-1}

CAS: [69618-95-7]

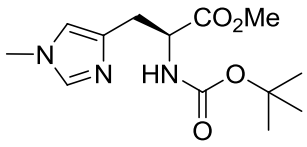
Yellow powder

Yield: 82%

^{1}H NMR (300.18 MHz, MeOD), ppm: 3.41 (2H, dd); 3.74 (3H, s); 3.94 (3H, s); 4.59 (1H, t); 7.47 (1H, s).

***N*-(*tert*-butoxycarbonyl)-1-methyl-L-histidine methyl ester; H2**

To a solution of compound **H1** (5g, 14.8 mmol) in the appropriate alcohol (50 mL) and acetonitrile (5 mL) was added diisopropylethylamine (2.6 mL, 14.8 mmol) and the solution was heated at 80°C for 24 h under nitrogen. The solvents were removed *in vacuo* and the residue dissolved in ethyl acetate. The solution was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to afford an oil which was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 4/1).



$C_{13}H_{21}N_3O_4$

M = 283.32 g.mol^{-1}

CAS : [72212-49-8]

Colorless oil

Yield: 73%

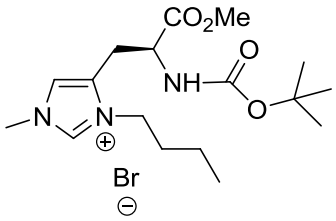
^{1}H NMR (300.18 MHz, MeOD), ppm: 1.41 (9H, s); 2.99 (2H, m); 3.60 (3H, s); 3.69 (3H, s); 4.50 (1H, dt, J_1=8.1 Hz, J_2=5.1 Hz); 5.89 (1H, d, J = 8 Hz); 6.62 (1H, s); 7.31 (1H, s).

6.2.1 General method for the synthesis of histidinium bromides.

To compound **H2** (3.3 mmol) is added *n*-butylbromide (3 mL). The reaction media was heated at 90°C overnight. The resulting biphasic mixture was concentrated *in vacuo* and dried over the vacuum line at 60°C for 10 hours to give yellow viscous oil.

(S)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-butyl-1-methyl-1H-imidazol-3-ium bromide; H3a

[mbHis-Boc-OMe]-[Br]



$C_{17}H_{30}BrN_3O_4$

M = 420.34 g.mol^{-1}

Yellow viscous, very hygroscopic

Yield: 95%.

DSC = -9.2°C (glass transition).

[α] $_D^{20}$ = -15.8 (c 1, MeOH).

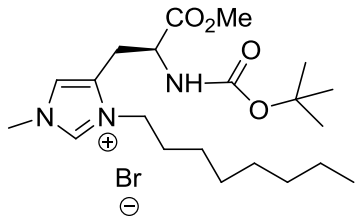
^{1}H NMR (300.18 MHz, MeOD), ppm: 0.96 (3H, t); 1.36 (9H, s); 1.33-1.47 (2H, m); 1.70-1.95 (2H, m); 3.15-3.35 (2H, m); 3.79 (3H, s); 4.03 (3H, s); 4.10-4.30 (2H, m); 4.50-4.65 (1H, m); 7.28 (1H, s); 8.91 (1H, s).

^{13}C NMR (75.48 MHz, MeOD), ppm: 12.49; 19.26; 25.52; 27.24; 31.48; 35.19; 46.66; 51.84; 52.22; 79.70; 121.67; 131.63; 156.39; 171.10.

Mass ESI+ (MeOH): 340; 284.

(S)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-1-methyl-3-octyl-1H-imidazol-3-ium bromide; H3b

[moHis-Boc-OMe]-[Br]



$C_{21}H_{38}BrN_3O_4$

M = 476.45 g.mol^{-1}

Yellow viscous oil

Yield: 98%.

DSC = -23.5°C (glass transition).

[α] $_D^{20}$ = -12.4 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 0.90 (3H, t); 1.31 (9H, s); 1.41 (12H, m); 1.88 (2H, m); 3.07-3.29 (1H, m); 3.78 (3H, s); 3.88 (3H, s); 4.17 (2H, m); 7.37 (1H, s); 8.92 (1H, s).

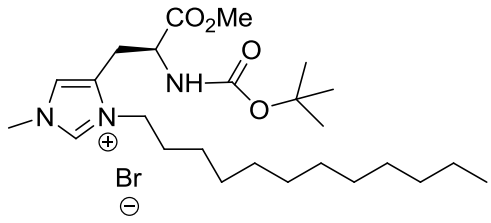
^{13}C NMR (75.48 MHz, MeOD), ppm: 13.06; 22.32; 26.06; 27.24; 28.77; 28.86; 29.51; 31.55; 35.14; 51.84; 52.23; 118.42; 121.68; 131.58; 171.08.

Mass ESI+ (MeOH): 396; 340.

Elemental Analysis, Calculated for $C_{21}H_{38}BrN_3O_4$: C, 52.94; H, 8.04; N, 8.82. Found: C, 52.73; H, 7.94; N, 8.77.

(S)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-dodecyl-1-methyl-1H-imidazol-3-ium bromide; H3c

[mDodecHis-Boc-OMe]-[Br]



$C_{25}H_{46}BrN_3O_4$

M = 532.55 g.mol^{-1}

Yellow viscous oil

Yield: 95%.

DSC = -37.3°C (glass transition).

[α] $_D^{20}$ = -10.5 (c 1, MeOH).

^{1}H NMR (300.18 MHz, Acetone-D6), ppm: 0.90 (3H, t); 1.30 (9H, s); 1.41 (18H, m); 2.06 (2H, m); 2.95 (1H, m); 3.37 (2H, m); 3.75 (3H, s); 4.06 (s, 3H); 4.38 (2H, m); 4.47 (1H, m); 7.72 (1H, s); 9.99 (1H, s).

^{13}C NMR (75.48 MHz, MeOD), ppm: 13.06; 22.36; 25.55; 26.05; 27.22; 28.80; 29.09; 29.29; 29.37; 31.70; 32.65; 33.04; 35.09; 51.82; 52.22; 81.60; 121.71; 131.66; 153.80; 171.04.

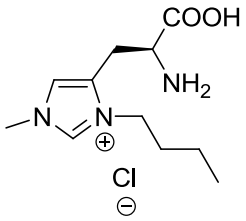
Mass ESI+ (MeOH): 452; 396.

Elemental Analysis, Calculated for $C_{25}H_{46}BrN_3O_4$: C, 56.38; H, 8.71; N, 7.89. Found: C, 56.49; H, 8.34; N, 7.59.

6.2.2 Complete deprotection of alkylated histidiniums

The protected amino acid derivative **H3a** (890 mg, 1.43 mmol) was heated at 70°C with 4.5 M HCl (3.5 mL) for 5h. After cooling, the aqueous phase was diluted with water (15 mL) and washed with diethylether. The aqueous phase was then evaporated under reduced pressure delivering pale yellow hydroscopic solid.

(S)-4-(2-amino-2-carboxyethyl)-3-butyl-1-methyl-1H-imidazol-3-ium chloride hydrochloride; H4 [mbHis]-[Cl]



$C_{11}H_{20}ClN_3O_2$

M = 261.75 g.mol^{-1}

Yellow solid

Yield: 95%.

[α] $_D^{20}$ = +8.7 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.84 (t, 3 H); 1.26 (m, 2 H); 1.74 (m, 2H); 3.26-3.41 (m, 2H); 3.76 (s, 3 H); 4.04 (t, 2 H); 4.23 (s, 1H); 7.37 (s, 1 H), 8.37 (s, 1 H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.72 (s); 18.89 (s); 23.83 (s); 31.01 (s); 35.85 (s); 46.89 (s); 51.42 (s); 53.99 (s); 122.62 (s); 128.46 (s); 168.68 (s).

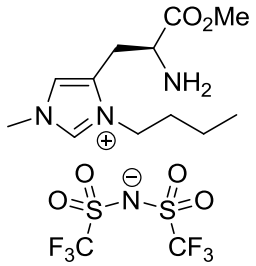
Mass ESI+ (MeOH): 226.

6.2.3 Boc- deprotection and the metathesis of histidinium methyl esters

A solution of HCl 1.25N in methanol (3.84 mL, 4.8 mmol) was added to a stirred solution of histidinium salt **H3a-b** (300 mg, 0.48 mmol) in dry methanol (5 mL). The mixture was stirred at room temperature for 3 hours. The solvents were evaporated and the residue partitioned between water and dichloromethane. After separation, the aqueous phase was concentrated under reduced pressure to afford the product as yellow oil. To the resulting oil was added 20 mL of water and bis(trifluoromethylsulfonyl)imide (1 eq., 0.48 mmol). Resulting mixture was neutralized to precipitate yellow oil-like compound, which was decanted, washed with distilled water and dried under vacuum line.

(*S*)-4-(2-amino-3-methoxy-3-oxopropyl)-1-methyl-3-octyl-1H-imidazol-3-ium bis(trifluoromethylsulfonyl)imide; H5a

[mbHis-OMe]-[NTf_2]



$C_{14}H_{22}F_6N_4O_6S_2$

M = 520.47 $g.mol^{-1}$

Yellow viscous oil

Yield: 57%.

DSC = -44.6°C (glass transition).

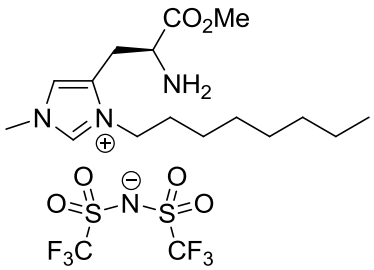
[α] $_D^{20}$ = +4.3 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 0.87 (t, 3 H); 1.28 (m, 2 H); 1.76 (m, 2H); 3.32-3.42 (m, 2H); 3.78 (s, 3 H); 3.80 (s, 3 H); 4.08 (t, 2 H); 4.40 (t, 1 H); 7.39 (s, 1 H), 8.73 (s, 1 H).

Mass ESI+ (MeOH): 240. **ESI-** (MeOH): 280.

(S)-4-(2-amino-3-methoxy-3-oxopropyl)-1-methyl-3-octyl-1H-imidazol-3-ium bis(trifluoromethylsulfonyl)imide; H5b

[moHis-OMe]-[NTf_2]



$C_{18}H_{30}F_6N_4O_6S_2$

M = 576.57 $g.mol^{-1}$

Yellow viscous oil

Yield: 60%.

DSC = -18.7°C (glass transition).

[α] $_D^{20}$ = +1.8 (c 1, MeOH).

^{1}H NMR (300.18 MHz, DMSO-D6), ppm: 0.85 (t, 3 H); 1.25 (m, 10 H); 1.73 (m, 2H); 3.30 (m, 2H); 3.18 (m, 1 H); 3.75 (s, 3 H); 3.80 (s, 3 H); 7.53 (s, 1 H), 9.09 (s, 1 H).

^{13}C NMR (75.48 MHz, $CDCl_3$), ppm: 16.96; 26.23; 28.50; 30.00; 32.71; 32.78; 33.43; 35.46; 39.15; 54.96; 56.35; 117.37-130.11 (q, 2C, J=311 Hz); 126.33; 126.61; 133.81; 174.07.

^{19}F NMR (282.37 MHz, MeOD), ppm: -79.5 (s).

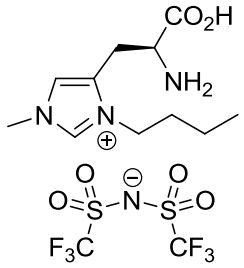
Mass ESI+ (MeOH): 296. **ESI-** (MeOH): 280.

6.2.4 One pot complete deprotection of histidiniums and ion metathesis

A solution of 1M HCl in water (2 eq.) was added to a stirred solution of histidinium bromide **H3a-c**. The mixture was stirred at room temperature for 3 hours. To resulting mixture was added KOH 1M water solution (2 eq.) and the mixture was stirred at room temperature for 3 hours. After that, 1 eq. of $LiNTf_2$ was added. The solution was stirred for 2 hours at room temperature. Then, it was neutralized to pH=7 using HCl solution to precipitate the oil-like yellow substance, which was separated from water layer, washed with distilled water and dried *in vacuo*.

(*S*)-4-(2-amino-2-carboxyethyl)-3-butyl-1-methyl-1H-imidazol-3-ium bis(trifluoromethylsulfonyl)imide; H6a

[mbHis]-[NTf_2]



$C_{13}H_{20}F_6N_4O_6S_2$

M = 506.44 $g.mol^{-1}$

CAS: 878484-87-8

Yellow viscous oil

Yield: 58%.

DSC = -16.6°C (glass transition).

[α] $_D^{20}$ = +0.9 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 1.05 (3H, t), 1.40-1.54 (4H, m), 1.90 (2H, m), 3.11 (1H, m), 3.91 (3H, s), 4.20 (2H, t), 7.39 (1H, s), 8.89 (1H, s).

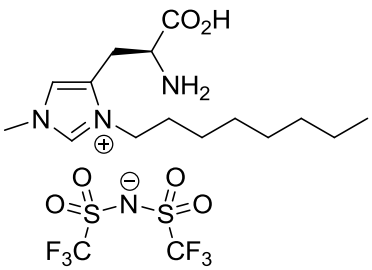
^{13}C NMR (75.48 MHz, MeOD), ppm: 12.42; 19.22; 25.91; 27.21; 31.45; 35.02; 52.48; 117.7; 121.64; 131.96; 172.55.

^{19}F NMR (282.37 MHz, $CDCl_3$), ppm: -78.8.

Mass ESI+ (MeOH): 226, 270. **ESI-** (MeOH): 280.

(S)-4-(2-amino-2-carboxyethyl)-1-methyl-3-octyl-1H-imidazol-3-ium bis(trifluoromethylsulfonyl)imide; H6b

[moHis]-[NTf_2]



$C_{17}H_{28}F_6N_4O_6S_2$

M = 562.55 $g.mol^{-1}$

Yellow viscous oil

Yield: 68%.

DSC = -29.6°C (glass transition).

[α] $_D^{20}$ = +2.3 (c 1, MeOH).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.93 (t, 3 H); 1.34-1.43 (m, 12 H); 1.90 (m, 2H); 3.33 (m, 2H); 3.78 (m, 1 H); 3.92 (s, 3 H); 7.45 (s, 1 H), 8,43 (s, 1 H).

^{13}C NMR (75.48 MHz, MeOD), ppm: 13.04 (s); 22.31 (s); 26.07 (s); 28.80 (s); 28.86 (s); 29.53 (s); 31.54 (s); 35.14 (s); 46.98 (s); 52.99 (s); 113.46-126.19 (q, 2C, J=320.4 Hz); 121.95 (s); 122.21 (s); 130.42 (s), 136.25 (s).

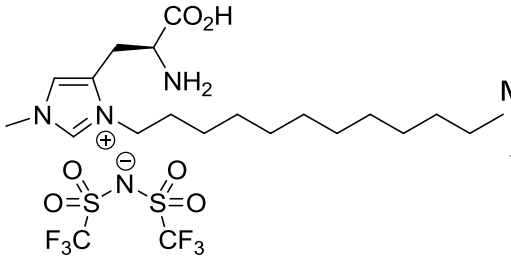
^{19}F NMR (282.37 MHz, MeOD), ppm: -79.5 (s).

Mass ESI+ (MeOH): 282. **ESI-** (MeOH): 280.

Elemental Analysis, Calculated for $C_{17}H_{28}F_6N_4O_6S_2$: C, 36.30; H, 5.02; N, 9.96. Found: C, 35.26; H, 4.80; N, 9.62.

(S)-4-(2-amino-3-methoxy-3-oxopropyl)-3-dodecyl-1-methyl-1H-imidazol-3-ium bis(trifluoromethylsulfonyl)imide; H6c

[mDodecHis]-[NTf_2]



$C_{21}H_{36}F_6N_4O_6S_2$

M = 618.65 g.mol^{-1}

Yellow viscous oil

Yield: 85%.

DSC = -28.5°C (glass transition).

[α] $_D^{20}$ = +0.9 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 0.89 (t, 3 H); 1.29-1.41 (m, 20 H); 1.87 (m, 2H); 3.07 (m, 1 H); 3.77 (s, 3 H); 4.16 (m, 2 H); 7.32 (s, 1 H), 8.83 (s, 1 H).

^{13}C NMR (75.48 MHz, MeOD), ppm: 13.08 (s); 22.37 (s); 26.07 (s); 27.23 (s); 27.29 (s); 28.80 (s); 29.10 (s); 29.28 (s); 29,29 (s); 29.37 (s); 31.07 (s); 35.00 (s); 46.80 (s); 52.95 (s); 117.72-121.96 (q, 2C, J=320.4 Hz); 117.72 (s); 121.72 (s); 131.65 (s); 132.18 (s), 173.57 (s).

^{19}F NMR (282.37 MHz, MeOD), ppm: -79.5 (s).

Mass ESI+ (MeOH): 338. **ESI-** (MeOH): 280.

Elemental Analysis, Calculated for $C_{21}H_{36}F_6N_4O_6S_2$: C, 40.77; H, 5.87; N, 9.06. Found: C, 40.46; H, 5.94; N, 8.84.

6.3 1,2-diaminocyclohexane (DACH) based compounds

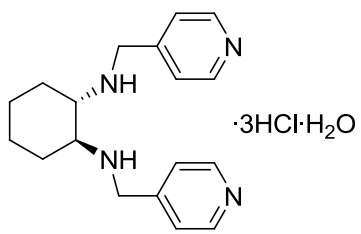
6.3.1 General procedure for synthesis of symmetric DACH-based compounds

To a stirred solution of 2- or 3- or 4-pyridylcarboxaldehyde (2 eq) in methanol, (1*S*,2*S*)-(+) or racemic -1,2-cyclohexanediamine (1 eq) in methanol was added slowly using a syringe pump. The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 15 min. The mixture was filtered and with stirring was added sodium borohydride (4 eq) in portions over a period of 30 min. The mixture was refluxed for 1 h, and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure leading to a white solid. The solid was dissolved in water, followed by addition of KOH 1M solution to pH≥10 and extracted successively three times with dichloromethane. The combined organic layer was dried with Na_2SO_4, filtered and slowly evaporated under reduced pressure, resulting in yellow oil (75-95% yield).

Purification by column chromatography on neutral SiO_2. Eluents: EtAc/MeOH/Et_3N = 88/10/2. After the column chromatography was carried out the preparation of hydrochlorides with 3 eq. of 1M HCl. Hydrochlorides were dried under vacuum and recrystallized from *i*-PrOH with total yield 30-60%.

Preparation of hydrochlorides was carried out by adding equivalent amount of HCl water solution to cyclohexane-1,2-diamine-based compound. Obtained mixtures were evaporated and dried under vacuum line.

(1S,2S)-N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D4,4-3HCl-H_2O



$C_{18}H_{29}Cl_3N_4O$

M = 423.807 g.mol^{-1}

Yellow solid

Yield: overall 25%.

Mp = 210°C.

[α] $_D^{20}$ = +64.5 (c 1, water).

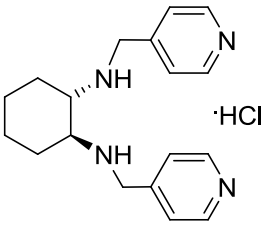
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.14-1.21 (m, 4 H); 1.67-1.76 (m, 2H); 2.12-2.26 (m, 2H); 2.75-2.84 (m, 2H); 4,16 (d, 2H, J=15,9); 4.38 (d, 2H, J= 15,9); 7.9 (d, 4H, J=6,3); 8,6 (d, 4H, J=6.3).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.8; 28.6; 59.9; 126.8; 141.8; 156.4.

Mass, CI (NH_3) (MeOH/H2O): 297.

Elemental Analysis, Calculated for $C_{18}H_{29}Cl_3N_4O$: C, 51.01; H, 6.90; N, 13.22. Found: C, 51.09; H, 7.18; N, 13.27.

(1S,2S)-N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine hydrochloride; D4,4-HCl



$C_{18}H_{25}ClN_4$

M = 332.87 g.mol^{-1}

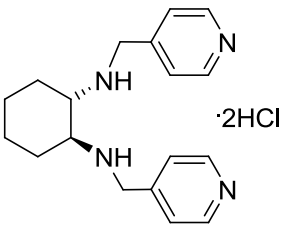
White solid

Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.33 (m, 4H); 1.86 (m, 2H); 2.30 (m, 2H); 2.88 (m, 2H); 4.20 (d, 2H, J=15.6 Hz); 4.41 (d, 2H, J=15.6 Hz); 7.90 (d, 2H, J=6.5 Hz); 8.70 (d, 2H, J=6.5 Hz).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.73; 28.62; 47.44; 59.56; 59.61; 125.73; 143.45; 154.26.

(1S,2S)-N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine bis-hydrochloride trihydrate; D4,4-2HCl-3H_2O



$C_{18}H_{32}Cl_2N_4O_3$

M = 423.38 g.mol^{-1}

White solid

Yield: 98%.

Mp = 146°C.

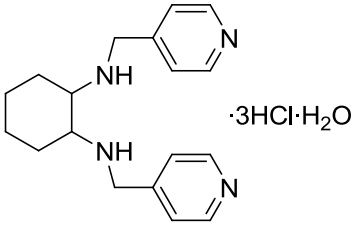
[α] $_D^{20}$ = +46 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.22 (m, 4H); 1.75 (m, 2H); 2.21 (m, 2H); 2.76 (m, 2H); 4.06 (d, 2H, J=15.5 Hz); 4.27 (d, 2H, J=15.5 Hz); 7.72 (d, 2H, J=6.5 Hz); 8.57 (d, 2H, J=6.5 Hz).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.73; 28.60; 47.39; 48.56; 58.83; 125.41; 141.44; 144.13.

Elemental Analysis, Calculated for $C_{18}H_{26}Cl_2N_4 \cdot 3H_2O$: C, 51.06; H, 7.62; N, 13.23. Found: C, 51.51; H, 7.57; N, 12.98.

N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D4,4Rac-3HCl-H_2O



$C_{18}H_{29}Cl_3N_4O$

M = 423.807 g.mol^{-1}

Beige solid

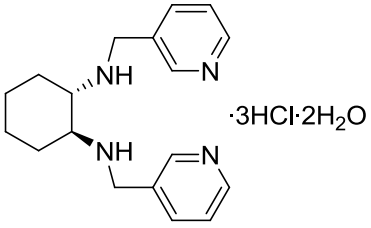
Yield: overall 20%.

Mp = 229°C.

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.17-1.49 (m, 4 H) ; 1.78-1.89 (m, 2H) ; 1.83 (m, 1H) ; 2.11 (m, 1H) ; 2.47 (m, 1H) ; 2.97 (m, 1H) ; 3.85 (d, 2H, J=14,0) ; 4.09 (d, 2H, J= 14,0) ; 7.52 (d, 4H, J=4,6) ; 8,55 (d, 4H, J=4.6).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.68; 28.70; 47.56; 59.95; 126.27; 141.88.

(1S,2S)-N^1,N^2-bis(pyridin-3-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate dehydrate; D3,3-3HCl-2H_2O



$C_{18}H_{31}Cl_3N_4O_2$

M = 441.82 g.mol^{-1}

White solid

Yield: overall 39%.

Mp = 243°C.

[α] $_D^{20}$ = +51.6 (c 1, water).

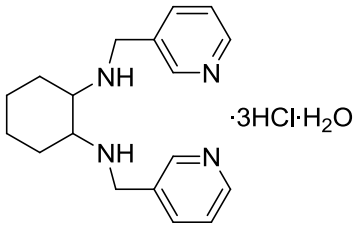
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.14-1.21 (m, 4 H); 1.67-1.76 (m, 2H); 2.12-2.26 (m, 2H); 2.83-2.84 (m, 2H); 4.12 (d, 2H, J=14.2); 4.35 (d, 2H, J= 14.2); 7.93 (dd, 2H, J_1=5.8, J_2=8.1); 8.51 (d, 2H, J=8.2); 8.65 (d, 2H, J=5.7); 8.74 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 21.9; 26.2; 45.1; 58.6; 127.4; 132.1; 141.7; 141.8; 147.8.

Mass, ES+ (MeOH/H_2O)**:** 297, 189, 147.

Elemental Analysis, Calculated for $C_{18}H_{31}Cl_3N_4O_2$: C, 48.93; H, 7.07; N, 12.68. Found: C, 48.62; H, 7.44; N, 12.57.

N^1,N^2-bis(pyridin-3-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D3,3Rac-3HCl-H_2O



$C_{18}H_{29}Cl_3N_4O$

M = 423.807 g.mol^{-1}

White solid

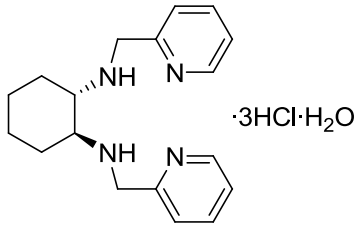
Yield: overall 49%.

Mp = 233°C.

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.2-1.41 (m, 4 H) ; 1.72-1.79 (m, 2H) ; 2.24-2.35 (m, 2H) ; 3.14 (m, 2H) ; 4.22 (d, 2H, J=14.0) ; 4.47 (d, 2H, J=14.0) ; 7.97 (dd, 2H, J=5.8); 8,58 (d, 2H, J=8.2) ; 8.69 (d, 2H, J=5.7), 8.7 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 22.38; 26.69; 45.42; 58.98; 127.78; 132.71; 142.13; 148.03.

(1S,2S)-N^1,N^2-bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D2,2-3HCl-H_2O



$C_{18}H_{29}Cl_3N_4O$

M = 423.80 g.mol^{-1}

Grey solid

Yield: overall 22%.

Mp = 190°C.

[α] $_D^{20}$ = +50.2 (c 1, water).

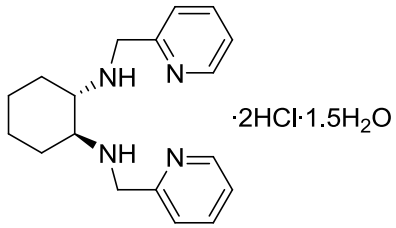
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.16-1.32 (m, 4 H) ; 1.64-1.78 (m, 2H) ; 2.20-2.29 (m, 2H) ; 2.83-2.94 (m, 2H) ; 4.17 (d, 2H, J=15.7); 4.40 (d, 2H, J=15.7); 6.57 (m, 2H); 7.64 (d, 2H, J=8.0); 8.11 (t, 2H, J=7.8); 8.42 (d, 2H, J=5.5).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.1; 28.1; 46.0; 59.5; 125.6; 125.8; 143.0; 144.5; 150.4.

Mass, CI (NH_3) (MeOH/H2O): 297.

Elemental Analysis, Calculated for $C_{18}H_{29}Cl_3N_4O$: C, 51.01; H, 6.90; N, 13.22, found: C, 51.00; H, 6.96; N, 13.11.

(1S,2S)-N^1,N^2-bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine dichlorohydrate, 1½ H_2O; D2,2-2HCl-½H_2O



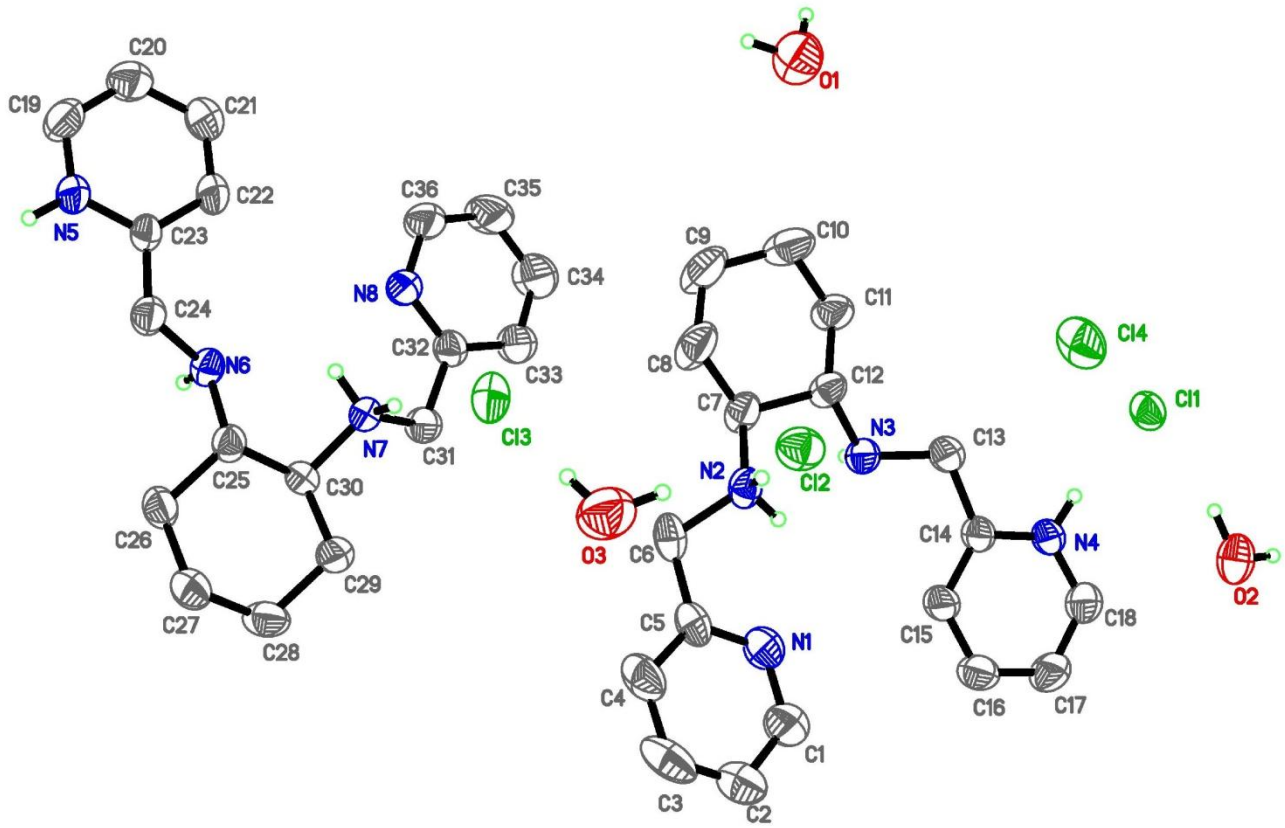
$C_{18}H_{26}Cl_2N_4$, 1.5H_2O

M = 369.33 g.mol^{-1}

Grey solid

Crystal Structure: monoclinic, space group *P 2$_1$*, a=16.8959(13)Å, b=7.2352(6)Å, c=17.3497(14)Å, β=96.293(4)°, α=γ=90°, V=2108.1(3)Å 3 , Z=2, crystal size 0.30 x 0.08 x 0.06 mm^3 , 40826 reflections collected (9233 independent, R int=0.0556), 502 parameters, 14

restraints, R1 [I>2σ(I)]=0.0480, wR2 [all data]=0.1126, absolute structure parameter: 0.02(5), largest diff. peak and hole: 0.302 and -0.264 e.Å^{-3}.



Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication n° CCDC-816872.

6.3.2 General procedure for synthesis of mixed DACH-based compounds

Was used the twice-repeated same method (as for synthesis of symmetric compounds) to obtain dissymmetric diamines.

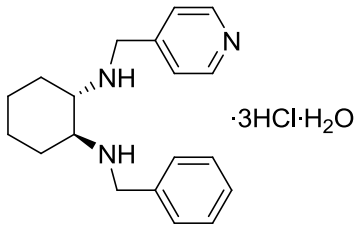
To a stirred solution of 2- or 3- or 4-pyridylcarboxaldehyde (2 eq) in methanol, (1*S*,2*S*)-(+) 1,2-cyclohexanediamine (1 eq) in methanol was added slowly using a syringe pump. The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 15 min. The mixture was filtered and with stirring was added sodium borohydride (2 eq) in portions over a period of 30 min. The mixture was refluxed for 1 h, and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure leading to a white solid. The solid was dissolved in water, followed by addition of KOH 1M solution to pH≥10 and extracted successively three

times with dichloromethane. The combined organic layer was slowly evaporated under reduced pressure, resulting in yellow oil (85-95% yield).

To a stirred solution of precedent compound (1 eq) in methanol was added slowly benzaldehyde (1 eq). The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 15 min. The mixture was filtered and with stirring was added sodium borohydride (2 eq) in portions over a period of 30 min. The mixture was refluxed for 1 h, and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure leading to a white solid. The solid was dissolved in water, followed by addition of KOH 1M solution to pH≥10 and extracted successively three times with dichloromethane. The combined organic layer was slowly evaporated under reduced pressure, resulting in yellow oil (75-85% yield).

Purification by column chromatography on neutral SiO_2. Eluents: EtAc/MeOH/Et_3N = 88/10/2 for bipyridinic compounds and 96/2/2 for products, containing phenyl cycle. After the column chromatography was carried out the preparation of hydrochlorides with 3 eq of 1M HCl. Hydrochlorides were dried under vacuum and recrystallized from *i*-PrOH with total yield 20-40%.

(1S,2S)-N^1-benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D4,Ph-3HCl-H_2O



$C_{19}H_{30}Cl_3N_3O$

M = 422.819 g.mol^{-1}

Beige solid

Yield: overall 21%.

Mp = 204°C.

[α] $_D^{20}$ = +57.8 (c 1, water).

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.18-1.51 (m, 4 H) ; 1.66-1.78 (m, 2H) ; 2.18-2.32 (m, 2H) ; 2.93-3.03 (m, 1H) ; 3.07-3.17 (m, 1H) 4.05 (dd, 2H, J_1=13.1, J_2=16.1) ; 4.29 (dd, 2H, J_1=13.1, J_2=16.1) ; 7.31 (m, 5H); 7.87 (d, 2H, J=6.7) ; 8.59 (d, 2H, J=6.7).

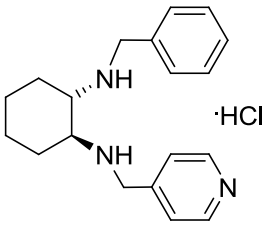
^{13}C NMR (75.48 MHz, D_2O), ppm: 22.56; 22.76; 26.31; 27.69; 47.70; 48.50; 58.21; 58.39;

126.52; 129.31; 129.73; 130.53; 136.92; 141.29; 156.16.

Mass, ES+ ($MeOH/H_2O$)**:** 296, 189, 147.

Elemental Analysis, Calculated for $C_{19}H_{30}Cl_3N_3O$: C, 53.97; H, 7.15; N, 9.94. Found: C, 54.17; H, 7.42; N, 9.93.

(1S,2S)-N^1-benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine hydrochloride; D4,Ph-HCl



$C_{19}H_{26}ClN_3$

M = 331.88 g.mol^{-1}

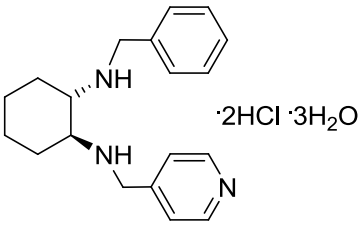
Brown solid

Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.90-1.41 (m, 4H); 1.56-1.70 (m, 2H) ; 2.10 (m, 2H); 2.47 (td, 1H, J_1=10,7 Hz; J_2= 3.7 Hz); 2.76 (td, 1H, J_1=10,7 Hz; J_2= 3.7 Hz); 3.74 (d, 1H, J=16.8 Hz); 3.90 (d, 1H, J=16.8 Hz); 3.99 (d, 1H, J=13.7 Hz); 4.17 (d, 1H, J=13.7 Hz); 7.68 (d, 2H, J=6.68 Hz); 8.44 (d, 2H, J=6.7 Hz).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.59; 23.96; 26.88; 30.13; 47.45; 48.12; 57.72; 59.48; 125.43; 129.33; 129.62; 131.16; 141.37; 141.39; 161.15.

(1S,2S)-N^1-benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine bis-hydrochloride trihydrate; D4,Ph-2HCl-3H_2O



$C_{19}H_{33}Cl_2N_3O_3$

M = 422.39 g.mol^{-1}

Beige solid

Yield: 100%.

Mp = 242°C.

[α] $_D^{20}$ = = +56 (c 1, H_2O).

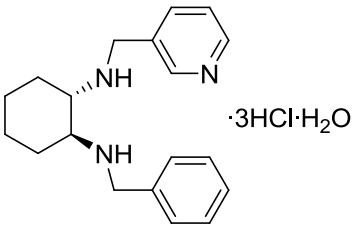
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.36-1.73 (m, 4H); 1.87 (m, 2H); 2.44 (m, 2H); 3.48 (m, 2H);

4.22 (d, 1H, J=13.0 Hz); 4.41 (d, 1H, J=15.4 Hz); 4.49 (d, 1H, J=13.0 Hz); 4.65 (d, 1H, J=15.4 Hz); 8.09 (d, 2H, J=6.8 Hz); 8.81 (d, 2H, J=6.8 Hz).

^{13}C NMR (75.48 MHz, D_2O), ppm: 24.84; 24.98; 28.72; 29.52; 50.12; 51.35; 60.41; 61.15; 129.28; 131.86; 132.32; 132.92; 144.07; 157.03.

Elemental Analysis, Calculated for $C_{19}H_{27}Cl_2N_3 \cdot 3H_2O$: C, 54.03; H, 7.87; N, 9.95. Found: C, 53.37; H, 7.26; N, 9.85.

(1S,2S)-N^1-benzyl-N^2-(pyridin-3-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D3,Ph-3HCl-H_2O



$C_{19}H_{30}Cl_3N_3O$

M = 422.819 g.mol^{-1}

White solid

Yield: overall 29%.

Mp = 225°C.

[α] $_D^{20}$ = +41.6 (c 1, water).

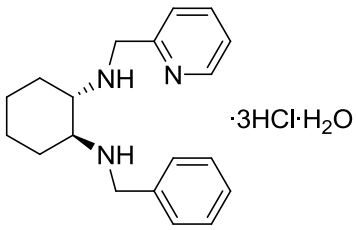
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.45 (m, 2H); 1.68 (m, 2H); 1.87 (m, 2H); 2.43-2.47 (m, 2H); 3.55 (m, 2H); 4.24 (d, 1H, J=13.0); 4.38 (d, 1H, J=13.7); 4.51 (d, 1H, J=13.0); 4.67 (d, 1H, J=13.7); 7.48 (m, 5H); 8.13 (dd, 1H, J1=5.8, J2=8.2); 8.74 (d, 1H, J=8.2); 8.86 (d, 1H, J=5.8); 8.95 (s, 1H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 22.04; 22.14; 26.00; 26.50; 45.42; 49.06; 57.74; 58.33; 127.75; 129.31; 129.84; 130.23; 132.81; 141.99; 142.02; 148.02.

Mass, ES+ (MeOH/H_2O)**:** 296, 189, 147.

Elemental Analysis, Calculated for $C_{19}H_{30}Cl_3N_3O$: C, 53.97; H, 7.15; N, 9.94. Found: C, 54.40; H, 7.28; N, 9.94.

(1S,2S)-N^1-benzyl-N^2-(pyridin-2-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate monohydrate; D2,Ph-3HCl-H_2O



$C_{19}H_{30}Cl_3N_3O$

M = 422.82 g.mol^{-1}

Light-violet solid

Yield: overall 21%.

Mp = 209°C.

[α] $_D^{20}$ = +41.3 (c 1, water).

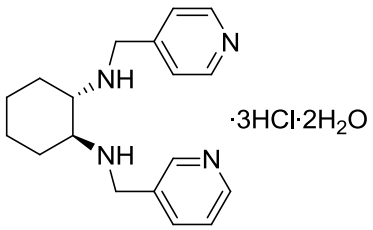
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.21-1.35 (m, 3 H) ; 1.44-1.55 (m, 1H) ; 1.77-1.89 (m, 2H) ; 2.27-2.36 (m, 2H) ; 2.84 (m, 1H) ; 3.13 (m, 1H) ; 4.13 (dd, 2H, J_1=16.5 ; J_2=13.2) ; 4.35 (dd, 2H, J_1=16.6; J_2=13.2) ; 7.37-7.45 (m, 5H); 7.76 (m, 2H) ; 8.31-8.40 (m, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.19; 23.46; 26.76; 29.67; 46.46; 47.80; 58.10; 59.19; 125.48; 125.63; 129.31; 129.71; 130.85; 141.88; 145.32; 153.34.

Mass, ES+ (MeOH/H_2O)**:** 296, 189, 144.

Elemental Analysis, Calculated for $C_{19}H_{30}Cl_3N_3O$: C, 53.97; H, 7.15; N, 9.94, found: C, 54.30; H, 7.48; N, 10.09.

(1S,2S)-N^1-(pyridin-3-ylmethyl)-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate dihydrate; D4,3-3HCl-2H_2O



$C_{18}H_{31}Cl_3N_4O_2$

M = 441.82 g.mol^{-1}

Beige solid

Yield: overall 29%.

Mp = 194°C.

[α] $_D^{20}$ = +65.6 (c 1, water).

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.16-1.38 (m, 4 H) ; 1.64-1.78 (m, 2H) ; 2.18-2.30 (m, 2H) ;

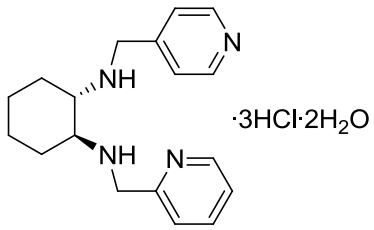
2.78-3.03 (m, 2H); 4.09 (d, 2H, J=16.2); 4.23 (d, 2H, J=14.0); 4.37 (d, 2H, J=16.2); 4.43 (d, 2H, J=14.0); 7.95 (m, 3H); 8.53 (d, 1H, J=8.4); 8.60-8.68 (m, 3H); 8.78 (s, 1H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.14; 27.43; 28.30; 45.07; 47.90; 59.29; 59.87; 126.49; 126.62; 127.67; 133.56; 141.33; 142.00; 147.47; 147.58.

Mass, ES+ (MeOH/H_2O)**:** 297, 189, 147.

Elemental Analysis, Calculated for $C_{18}H_{31}Cl_3N_4O_2$: C, 48.93; H, 7.07; N, 12.68. Found: C, 48.13; H, 7.90; N, 12.43.

(1S,2S)-N^1-(pyridin-2-ylmethyl)-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate dihydrate; D4,2-3HCl-2H_2O



$C_{18}H_{31}Cl_3N_4O_2$

M = 441.82 g.mol^{-1}

Beige solid

Yield: overall 20%.

Mp = 173°C.

[α] $_D^{20}$ = +44 (c 1, H_2O).

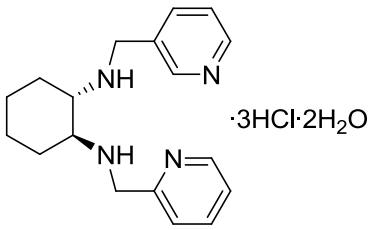
^{1}H NMR (300.18 MHz, D_2O), ppm: 1.12-1.39 (m, 4 H) ; 1.66-1.79 (m, 2H) ; 2.16-2.31 (m, 2H) ; 2.73 (m, 1H) ; 3.00 (m, 1H) ; 4.05 (d, 1H, J1=16.3); 4.35 (d, 1H, J=15.4); 4.37 (d, 1H, J=16.3); 4.57 (d, 1H, J=15.4); 7.66 (m, 2H); 8.02 (d, 2H, J=6.6); 8.22 (t, 1H, J=7.9); 8.42 (d, 1H, J=5.1); 8.70 (d, 2H, J=6.7).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.35; 23.44; 26.90; 29.84; 46.65; 46.91; 58.66; 61.55; 125.75; 126.09; 127.21; 141.36; 141.84; 146.08; 152.63; 153.44.

Mass,ES+ (MeOH/H_2O)**:** 297, 313, 388.

Elemental Analysis, Calculated for $C_{18}H_{31}Cl_3N_4O_2$: C, 48.93; H, 7.07; N, 12.68, found: C, 48.73; H, 6.78; N, 11.89.

(1S,2S)-N^1-(pyridin-2-ylmethyl)-N^2-(pyridin-3-ylmethyl)cyclohexane-1,2-diamine trichlorohydrate dihydrate; D3,2-3HCl-2H_2O



$C_{18}H_{31}Cl_3N_4O_2$

M = 441.82 $g.mol^{-1}$

White solid

Yield: overall 29%.

Mp = 221°C.

[α] $_D^{20}$ = +60.9 (c 1, water).

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.08-1.47 (m, 4 H) ; 1.64-1.80 (m, 2H) ; 2.21-2.32 (m, 2H) ; 2.68 (m, 1H) ; 3.04 (m, 1H) ; 4.03 (d, 1H, J_1=16.2) ; 4.33 (dd, 2H, J_1=16.3, J_2=13.8) ; 4.54 (d, 1H, J_2=13.8) ; 7.74 (dd, 2H, J_1=16.8 ; J_2=17.5); 8.00 (t, 1H, J=6.5) ; 8.25 (t, 1H, J=8.3) ; 8.40 (d, 1H, J=6.0), 8.58 (d, 1H ; J=8.1) ; 8.73 (d, 1H, J=8.0) ; 8.84 (s, 1H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.26; 23.35; 26.76; 29.67; 44.51; 46.84; 58.60; 61.19; 125.83; 126.19; 127.91; 131.86; 141.33; 142.35; 146.19; 148.36; 153.10.

Mass, ES+ (MeOH/H_2O)**:** 297, 189, 144.

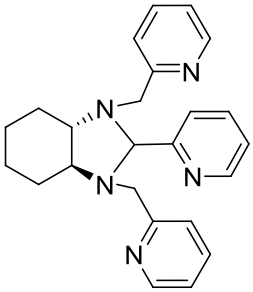
Elemental Analysis, Calculated for $C_{18}H_{31}Cl_3N_4O_2$: C, 48.93; H, 7.07; N, 12.68, found: C, 48.96; H, 7.29; N, 12.59.

6.3.3 Protected DACH-based compounds

To a stirred solution of 1,2-cyclohexanediamine-based compound in dichloromethane was added corresponded freshly distilled pyridylcarboxaldehyde or benzaldehyde. The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 3 hours. The mixture was filtered, evaporated under reduced pressure, and dried in vacuum line, resulting in yellow oil.

Purification (if necessary) was performed by column chromatography on basic Al_2O_3. Eluents: EtAc/CH_2Cl_2 = 3/1.

(3aS,7aS)-2-(pyridin-2-yl)-1,3-bis(pyridin-2-ylmethyl)octahydro-1H-benzo[d]imidazole; D2,2,2



$C_{24}H_{27}N_5$

M = 385.50 g.mol^{-1}

Yellow oil

Yield: overall 10.3%.

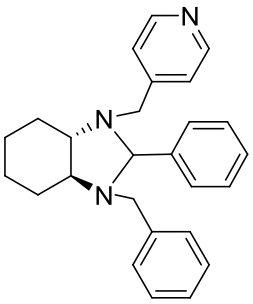
[α] $_D^{20}$ = +58 (c 1, CH_2Cl_2).

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 1.24 (m, 4H) ; 1.66 (m, 4H) ; 2.57 (m, 1H) ; 2.94 (m, 1H) ; 3.59 (dd, 2H, J_1=8.6, J_2=23.7) ; 3.91 (dd, 2H, J_1=14.3, J_2=28.6) ; 4.87 (s, 1H); 6.92 (m, 1H) ; 6.99 (m, 1H); 7.17 (m, 1H), 7.33 (m, 1H) ; 7.37 (m, 2H) ; 7.47 (m, 2H); 8.30 (m, 3H).

^{13}C NMR (75.48 MHz, $CDCl_3$), ppm: 24.43; 29.82; 30.07; 54.77; 58.73; 67.56; 69.19; 87.83; 121.45; 121.61; 122.33; 122.64; 123.59; 123.91; 135.63; 135.67; 136.02; 148.34; 148.43; 148.48; 159.72; 160.95; 161.15.

Mass, Chem. Ioniz. by NH_3 (CH_2Cl_2): 386.

(3aS,7aS)-1-benzyl-2-phenyl-3-(pyridin-4-ylmethyl)octahydro-1H-benzo[d]imidazole; D2,Ph,Ph



$C_{26}H_{29}N_3$

M = 383.53 g.mol^{-1}

Yellow oil

Yield: 99%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 1.17 (m, 4H) ; 1.63 (m, 4H) ; 2.42 (m, 1H) ; 2.74 (m, 1H) ; 3.20 (m, 1H) ; 3.44-3.74 (m 3H); 6.94-7.27 (m, 12H); 8.28 (m, 2H).

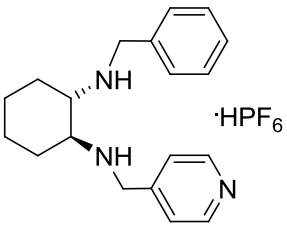
6.3.4 Preparation of salts of DACH-based compounds

Corresponding cyclohexane-1,2-diamine-based compound in the form of hydrochloride hydrate was added to 1M water solution of KOH to obtain pH ≥ 12. Resulting mixture was extracted 3 times with CH_2Cl_2. Combined organic layers were evaporated and dried under vacuum line.

Preparation of hexafluorophosphates and tetrafluoroborates was carried out by adding equivalent amount of corresponding acid in water solution to cyclohexane-1,2-diamine-based compound. Obtained mixture was stirred for 30 minutes, evaporated and dried under vacuum line.

Preparation of bis(trifluoromethanesulfonyl)imides was carried out by adding equivalent amount of bis(trifluoromethanesulfonyl)imide in $CHCl_3$. Obtained mixture was stirred for 30 minutes, evaporated and dried under vacuum line.

(1S,2S)-N^1-benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine hexafluorophosphate; D4,Ph-HPF_6



$C_{19}H_{26}F_6N_3P$

M = 441.39 $g.mol^{-1}$

Brown solid

Yield: 100%.

T_G = -18.7°C, **Mp** = 79°C.

[α] $_D^{20}$ = +40.1 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 1.13-1.54 (m, 4H); 1.87 (m, 2H); 2.34 (m, 2H); 2.62 (td, 1H, J_1=10.8, J_2=3.9); 2.89 (td, 1H, J_1=11.1, J_2=3.8); 3.85 (d, 1H, J=15.6 Hz); 4.16 (d, 1H, J=15.6 Hz); 4.24 (d, 1H, J=13.2 Hz); 4.34 (d, 1H, J=13.2 Hz); 7.43-7.53 (m, 5H); 7.77 (d, 2H, J=6.0 Hz); 8.61 (d, 2H, J=5.8 Hz).

^{13}C NMR (75.48 MHz, MeOD), ppm: 23.83; 24.12; 27.14; 30.20; 48.45; 58.14; 60.12; 124.60; 129.06; 129.25; 129.38; 131.64; 145.07; 149.47.

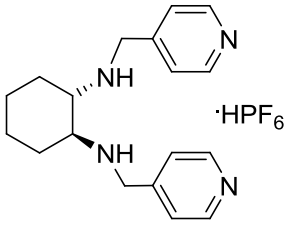
^{31}P NMR (121.49 MHz, MeOD), ppm: -143.2 (sept, J=708.5 Hz).

^{19}F NMR (282.37 MHz, MeOD), ppm: -72.7 (d, J=708.8 Hz).

Mass, CI+ (NH_3) (MeOH): 296, 205; **CI- (NH_3)** (MeOH): 150, 219, 125.

HRMS: Calculated for $C_{19}H_{26}N_3$ (M + H+): 296.2127; found: 296.2117.

(1S,2S)-N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine hexafluorophosphate; D4,4-HPF_6



$C_{18}H_{25}F_6N_4P$

M = 442.38 g.mol^{-1}

Brown solid

Yield: 100%.

T_G = -19.1°C, **Mp** = 81°C.

[α] $_D^{20}$ = +41.7 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 1.36-1.41 (m, 4H); 1.84 (m, 2H); 2.33 (m, 2H); 2.74 (m, 2H); 4.07 (d, 2H, J=14.5 Hz); 4.25 (d, 2H, J=14.3 Hz); 7.60 (d, 4H, J=5.5 Hz); 8.59 (s, 4H).

^{13}C NMR (75.48 MHz, MeOD), ppm: 23.96; 28.66; 59.52; 124.23; 148.20; 154.28.

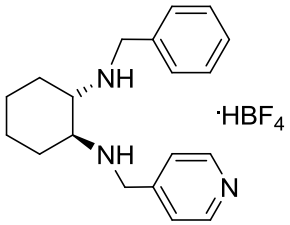
^{31}P NMR (121.49 MHz, MeOD), ppm: -143.2 (sept, J=708.6 Hz).

^{19}F NMR (282.37 MHz, MeOD), ppm: -72.7 (d, J= 708.7 Hz).

Mass, CI+ (NH_3) (MeOH): 297, 206.

HRMS: Calculated for $C_{18}H_{25}N_4$: 297.2079; found: 297.2072.

(1S,2S)-N^1-benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine tetrafluoroborate; D4,Ph-HBF_4



$C_{19}H_{26}BF_4N_3$

M = 383.23 g.mol^{-1}

Brown solid

Yield: 99%.

Mp = 99°C.

[α] $_D^{20}$ = +69.7 (c 1, MeOH).

^{1}H NMR (300.18 MHz, MeOD), ppm: 1.04-1.52 (m, 4H); 1.81 (m, 2H); 2.27 (m, 2H); 2.49 (dt, 1H, J_1=11Hz, J_2=4 Hz); 2.79 (dt, 1H, J_1=11Hz, J_2=4 Hz); 3.72 (d, 1H, J= 14.7 Hz); 3.98 (d, 1H, J= 14.7 Hz); 4.21 (AB, 2H, δΔ=0.094, J_{AB}=13.2); 7.42 (m, 6H); 8.45 (d, 2H, J=6.2 Hz).

^{13}C NMR (75.48 MHz, MeOD), ppm: 23.90; 24.20; 27.23; 30.18; 58.10; 60.22; 123.93; 129.02; 129.18; 129.32; 131.91; 147.50; 152.19.

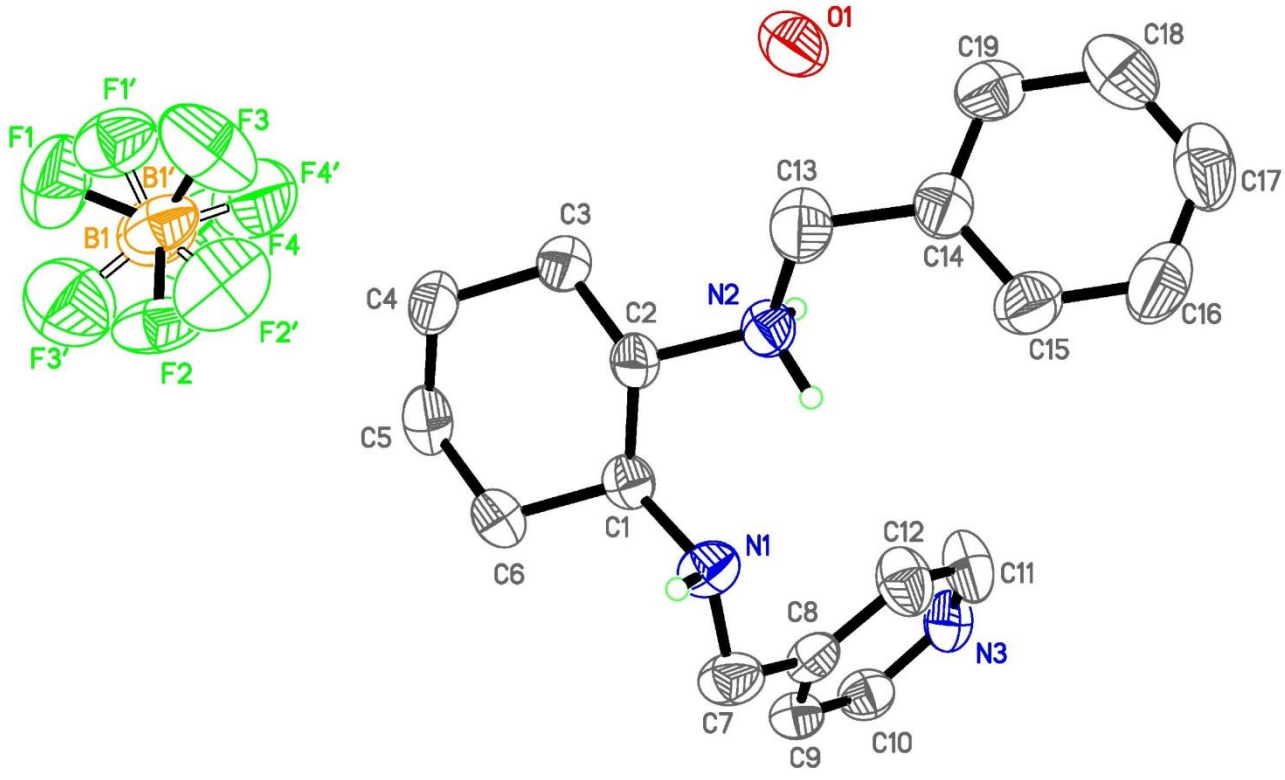
^{31}B NMR (96, 29 MHz, MeOD), ppm: -0.83 (s).

^{19}F NMR (282.37 MHz, MeOD), ppm: -154.0 (s).

Mass, ES+ (MeOH)**:** 296, 313, 216. **ES-** (MeOH)**:** 87.

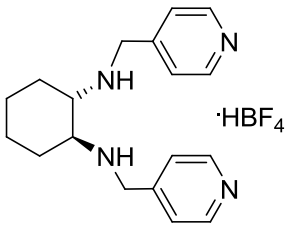
Elemental Analysis, Calculated for $C_{19}H_{26}BF_4N_3$: C, 59.55; H, 6.84; N, 10.96. Found: C, 59.16; H, 6.68; N, 10.74.

Crystal Structure: monoclinic, space group *P 2$_1$*, a=9.2754(13)Å, b=8.9032(12)Å, c=12.8665(19)Å, β=110.149(6)°, α=γ=90°, V=997.5(2)Å 3 , Z=2, crystal size 0.18 x 0.15 x 0.13 mm^3 , 14677 reflections collected (4018 independent, R int=0.0267), 308 parameters, 177 restraints, R1 [I>2σ(I)]=0.0537, wR2 [all data]=0.1350, largest diff. peak and hole: 0.265 and −0.255 e.Å^{-3} .



Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-816873.

(1S,2S)-N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine tetrafluoroborate; D4,4-HBF_4



$C_{18}H_{25}BF_4N_4$

M = 384.22 $g.mol^{-1}$

Yellow solid

Yield: 100%.

Mp = 113°C.

$[\alpha]_D^{20}$ = +58.5 (c 1, MeOH).

^{1}H NMR (300.18 MHz, DMSO-D6), ppm: 1.22 (m, 4H); 1.73 (m, 2H); 2.17 (m, 2H); 2.66 (m, 2H); 4.00 (d, 2H, J=14.6 Hz); 4.17 (d, 2H, J=14.6 Hz); 7.60 (d, 4H, J=6.1 Hz); 8.67 (d, 4H, J=6.1 Hz).

^{13}C NMR (75.48 MHz, DMSO-D6), ppm: 24.27; 28.79; 47.46; 58.98; 124.51; 147.63; 148.97.

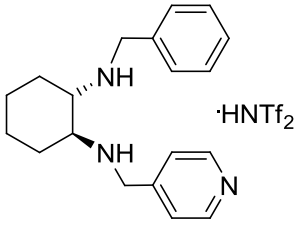
^{11}B NMR (96, 29 MHz, DMSO-D6), ppm: -1.3 (s).

^{19}F NMR (282.37 MHz, DMSO-D6), ppm: -148.1 (s).

Mass, ES+ (MeOH)**:** 297, 313, 189. **ES-** (MeOH): 87.

Elemental Analysis, Calculated for $C_{18}H_{25}BF_4N_4$: C, 56.27; H, 6.56; N, 14.58. Found: C, 56.18; H, 6.46; N, 14.36.

(1S,2S)-N^1-benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine bis(trifluoromethanesulfonyl)imide; D4,Ph-$HNTf_2$



$C_{21}H_{26}F_6N_4O_4S_2$

M = 576.57 $g.mol^{-1}$

Yellow viscous wax

Yield: 100%.

DSC = +0.3°C (glass transition).

[α] $_D^{20}$ = +36.2 (c 1, MeOH).

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 0.95-1.54 (m, 4H); 1.80 (m, 2H); 2.17 (m, 2H); 2.44 (m, 1H); 2.41 (m, 1H); 3.62 (d, 1H, J=14.0 Hz); 3.83 (d, 1H, J=14.0 Hz); 4.04 (d, 1H, J=13.2 Hz); 4.18 (d, 1H, J=13.2 Hz); 7.19 (d, 2H, J=5.9 Hz); 7.36 (m, 5H); 8.15 (d, 2H, J=5.9 Hz).

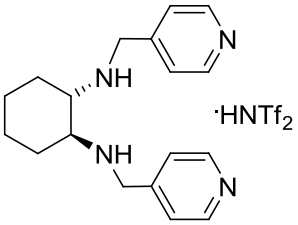
^{13}C NMR (75.48 MHz, CD_3CN), ppm: 24.02; 24.26; 27.28; 30.55; 48.58; 48.68; 57.74; 60.69; 113.35-126.11 (q, 2C, J=317 Hz); 123.95; 129.35; 129.72; 130.09; 130.64; 148.42; 149.78.

^{19}F NMR (282.37 MHz, CD_3CN), ppm: -80.15 (s).

Mass, ES+ (MeOH)**:** 296, 313, 216. **ES-** (MeOH): 280.

Elemental Analysis, Calculated for $C_{21}H_{26}F_6N_4O_4S_2$: C, 43.75; H, 4.55; N, 9.72. Found: C, 44.23; H, 4.85; N, 9.34.

(1S,2S)-N^1,N^2-bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine bis(trifluoromethanesulfonyl)imide; D4,4-HNTf$_2$



$C_{20}H_{25}F_6N_5O_4S_2$

M = 577.56 g.mol^{-1}

Yellow viscous wax

Yield: 100%.

DSC = +5.1°C (glass transition).

[α] $_D^{20}$ = +38.5 (c 1, MeOH).

^{1}H NMR (300.18 MHz, CD_3CN), ppm: 1.31 (m, 4H); 1.84 (m, 2H); 2.33 (m, 2H); 2.64 (m, 2H); 3.93 (d, 2H, J=14.1 Hz); 4.18 (d, 2H, J=14.1 Hz); 7.40 (d, 4H, J=6.0 Hz); 8.57 (d, 4H, J=6.0 Hz).

^{13}C NMR (75.48 MHz, CD_3CN), ppm: 23.9; 28.48; 47.57; 59.60; 120.12 (q, 2C, J=320 Hz); 123.78; 145; 149.76.

^{19}F NMR (282.37 MHz, CD_3CN), ppm: -80.12 (s).

Mass, ES+ (MeOH)**:** 297, 313, 189. **ES-** (MeOH): 280.

Elemental Analysis, Calculated for $C_{20}H_{25}F_6N_5O_4S_2$: C, 41.59; H, 4.36; N, 12.13. Found: C, 41.45; H, 4.31; N, 11.82.

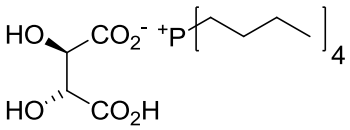
6.4 Tetrabutylphosphonium tatrates

Before the synthesis, commercial $[PBu_4]OH$ needs to be purified from $[PBu_4]Cl$. To do this, it was extracted by CH_2Cl_2, dried under reduced pressure (only in order to eliminate residue of organic solvent), diluted with distilled water and titrated with HCl to determine exact concentration.

To the tartaric acid was added appropriate volume of solution $[PBu_4]OH$. Resulting mixture was stirred for 15 minutes; evaporated to dryness under reduced pressure and dried under the vacuum line.

Tetrabutylphosphonium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate; T(*R,R*)-P_4

[PBu_4]-[(*R,R*)-Trtr]



$C_{20}H_{41}O_6P$

M = 408.50 $g.mol^{-1}$

White wax

Yield: overall 100%.

DSC = -42.2°C (glass transition).

[α] $_D^{20}$ = +9.3 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.75 (t, 12 H) ; 1.23-1.43 (m, 16 H) ; 1.98 (m, 8H) ; 4.35 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.54 (s); 17.32-17.96 (d, J= 50.2); 22.68-22.74 (d, J= 4.5); 23.20-23.40 (d, J= 13.5), 72.80 (s); 176.29 (s).

^{31}P NMR (121.49 MHz, D_2O), ppm: 33.24 (s).

Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.

IR (CaF_2, cm^{-1}): 3317, 2960, 1609, 1411, 1307.

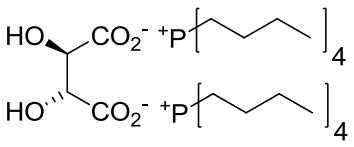
Water content (Karl Fisher): 8.1%.

Traces Cl: 146 ppm.

Elemental Analysis, Calculated for $C_{20}H_{41}O_6P \cdot 2H_2O$: C, 54.04; H, 10.20. Found: C, 54.71; H, 9.88.

Tetrabutylphosphonium (2*R*,3*R*)-2,3-dihydroxysuccinate; T(*R,R*)-2P$_4$

[PBu$_4$]$_2$-[(*R,R*)-Trtr]



$C_{36}H_{76}O_6P_2$

M = 666.93 g.mol^{-1}

White wax

Yield: overall 100%.

DSC = -62.1°C (glass transition).

[α] $_D^{20}$ = +7.7 (c 1,).

^{1}H NMR (300.18 MHz, D$_2$O), ppm: 1.03 (t, 24 H) ; 1.50-1.71 (m, 32 H) ; 2.25 (m, 16H) ; 4.41 (s, 2H).

^{13}C NMR (75.48 MHz, D$_2$O), ppm: 12.54 (s); 17.33-17.97 (d, J= 48.5); 22.69-22.75 (d, J= 4.5); 23.20-23.40 (d, J= 15.2), 72.83 (s); 178.40 (s).

^{31}P NMR (121.49 MHz, D$_2$O), ppm: 33.24 (s).

Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.

IR (CaF$_2$, cm^{-1}): 3351, 2959, 1609, 1350.

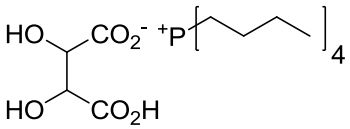
Water content (Karl Fisher): 13.9%.

Traces Cl: 968 ppm.

Elemental Analysis, Calculated for $C_{36}H_{76}O_6P_2 \cdot 6H_2O$: C, 55.79; H, 11.14. Found: C, 56.20; H, 11.31.

Tetrabutylphosphonium-3-carboxy-2,3-dihydroxypropanoate; T(Rac)-P_4

[PBu_4]-[(Rac)-Trtr]



$C_{20}H_{41}O_6P$

M = 408.50 g.mol^{-1}

White wax

Yield: overall 100%.

DSC = -44.2°C (glass transition).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.76 (t, 12 H) ; 1.23-1.43 (m, 16 H) ; 1.99 (m, 8H) ; 4.33 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.54 (s); 17.32-17.96 (d, J= 48.3); 22.68-22.74 (d, J= 4.5); 23.19-23.40 (d, J= 15.2), 72.91 (s); 176.49 (s).

^{31}P NMR (121.49 MHz, D_2O), ppm: 33.24 (s).

Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.

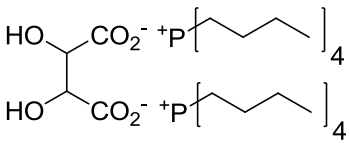
Water content (Karl Fisher): 4.2%.

Traces Cl: 171ppm.

Elemental Analysis, Calculated for $C_{20}H_{41}O_6P \cdot H_2O$: C, 56.32; H, 10.16. Found: C, 55.88; H, 10.15.

Tetrabutylphosphonium-2,3-dihydroxysuccinate; T(Rac)-2P_4

[PBu_4]$_2$-[(Rac)-Trtr]



$C_{36}H_{76}O_6P_2$

M = 666.93 g.mol^{-1}

White wax

Yield: overall 100%.

Mp = +71.7°C.

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.76 (t, 24 H) ; 1.20-1.40 (m, 32 H) ; 1.99 (m, 16H) ; 4.14 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.53 (s); 17.32-17.96 (d, J= 48.2); 22.68-22.74 (d, J= 4.5); 23.19-23.40 (d, J= 15.3), 72.84 (s); 178.40 (s).

^{31}P NMR (121.49 MHz, D_2O), ppm: 33.24 (s).

Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.

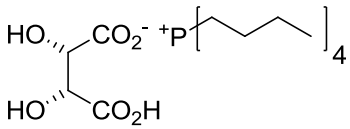
Water content (Karl Fisher): 9.7%.

Traces Cl: 114 ppm.

Elemental Analysis, Calculated for $C_{36}H_{76}O_6P_2 \cdot 4H_2O$: C, 58.51; H, 11.46. Found: C, 58.75; H, 11.50.

Tetrabutylphosphonium-(2*R*,3*S*)-3-carboxy-2,3-dihydroxypropanoate; T(*R,S*)-P_4

[PBu_4]-[(*R,S*)-Trtr]



$C_{20}H_{41}O_6P$

M = 408.50 g.mol^{-1}

White wax

Yield: overall 100%.

DSC = -47.8°C (glass transition).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.75 (t, 12 H) ; 1.2-1.4 (m, 16 H) ; 1.98 (m, 8H) ; 4.29 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.53 (s); 17.32-17.96 (d, J= 48.3); 22.67-22.73 (d, J= 4.5); 23.19-23.39 (d, J= 15.3), 73.64 (s); 175.52 (s).

^{31}P NMR (121.49 MHz, D_2O; H coupled), ppm: 33.23 (m).

Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.

IR (CaF_2, cm^{-1}): 3418, 2959, 1597, 1466, 1356.

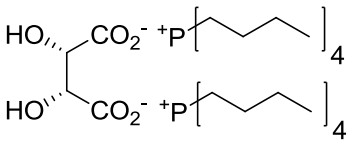
Water content (Karl Fisher): 4.2%.

Traces Cl: 479 ppm.

Elemental Analysis, Calculated for $C_{20}H_{41}O_6P \cdot H_2O$: C, 56.32; H, 10.16. Found: C, 55.37; H, 9.73.

Tetrabutylphosphonium-(2*R*,3*S*)-3-carboxy-2,3-dihydroxypropanoate; T(*R,S*)-2P$_4$

[PBu$_4$]$_2$-[(*R,S*)-Trtr]



$C_{36}H_{76}O_6P_2$

M = 666.93 g.mol^{-1}

White wax

Yield: overall 100%.

DSC = -68.2°C (glass transition).

^{1}H NMR (300.18 MHz, D$_2$O), ppm: 0.76 (t, 24 H) ; 1.20-1.40 (m, 32 H) ; 1.99 (m, 16H) ; 4.05 (s, 2H).

^{13}C NMR (75.48 MHz, D$_2$O), ppm: 12.55 (s); 17.32-17.96 (d, J= 48.3); 22.68-22.74 (d, J= 4.5); 23.19-23.40 (d, J= 15.3), 72.81 (s); 177.16 (s).

^{31}P NMR (121.49 MHz, D$_2$O), ppm: 33.24 (s).

Mass, FAB (glycerol); **FAB<0:** 149; **FAB>0**: 259.

IR (CaF$_2$, cm^{-1}): 3304, 2959, 1614, 1465, 1348.

Water content (Karl Fisher): 7.5%.

Traces Cl: 462 ppm.

Elemental Analysis, Calculated for $C_{36}H_{76}O_6P_2 \cdot 3H_2O$: C, 59.97; H, 11.46. Found: C, 59.64; H, 11.59.

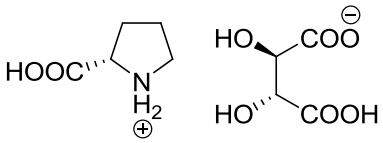
6.5 Prolinium tartrates

6.5.1 General procedure of prolinium tartrates preparation

Amino acid proline ((*R*), (*S*) or racemic; 1 or 2 eq.) was added to the water solution of tartaric acid ((*R,R*) or (*S,S*) 1 eq.). Resulting solution was stirred for 1 hour, evaporated and dried under vacuum line.

(S)-2-carboxypyrrolidinium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate; T(*R,R*)-Pro(*S*)

[(*S*)-Pro]-[(*R,R*)-Trtr]



$C_9H_{15}NO_8$

M = 265.22 g.mol^{-1}

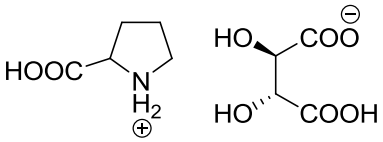
White solid

Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 2.00 (m, 3H); 2.32 (m, 1H); 3.24 (m, 2H); 4.16 (m, 1H); 4.68 (s, 2H).

2-carboxypyrrolidinium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate; T(*R,R*)-Pro(Rac)

[Pro]-[(*R,R*)-Trtr]



$C_9H_{15}NO_8$

M = 265.22 g.mol^{-1}

White solid

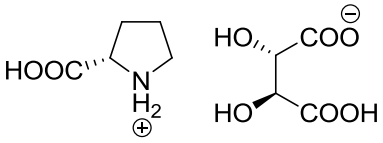
Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 2.00 (m, 3H); 2.32 (m, 1H); 3.34 (m, 2H); 4.16 (m, 1H); 4.69 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.63; 28.78; 46.09; 60.80; 72.06; 173.97; 174.90.

(S)-2-carboxypyrrolidinium (2*S*,3*S*)-3-carboxy-2,3-dihydroxypropanoate; T(*S,S*)-Pro(*S*)

[(*S*)-Pro]-[(*S,S*)-Trtr]



$C_9H_{15}NO_8$

M = 265.22 g.mol^{-1}

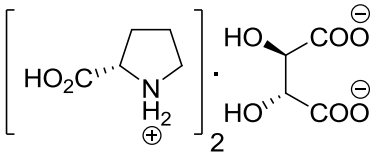
White solid

Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 2.02 (m, 3H); 2.35 (m, 1H); 3.37 (m, 2H); 4.16 (m, 1H); 4.68 (s, 2H).

Bis((S)-2-carboxypyrrolidinium)-(2*R*,3*R*)-2,3-dihydroxysuccinate); T(*R,R*)-2Pro(*S*)

[(*S*)-Pro]$_2$-[(*R,R*)-Trtr]



$C_{14}H_{24}N_2O_{10}$

M = 380.35 g.mol^{-1}

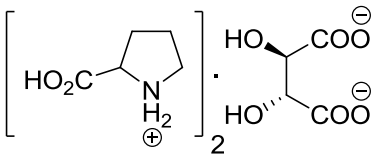
White solid

Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 2.04 (m, 3H); 2.35 (m, 1H); 3.34 (m, 2H); 4.14 (m, 1H); 4.66 (s, 2H).

Bis(2-carboxypyrrolidinium)-(2*R*,3*R*)-2,3-dihydroxysuccinate) ; T(*R,R*)-2Pro(Rac)

[Pro]$_2$-[(*R,R*)-Trtr]



$C_{14}H_{24}N_2O_{10}$

M = 380.35 g.mol^{-1}

White solid

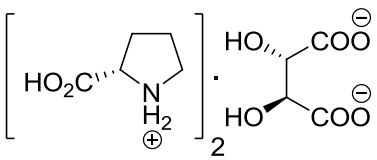
Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.99 (m, 3H); 2.31 (m, 1H); 3.31 (m, 2H); 4.11 (m, 1H); 4.63 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 23.66; 28.83; 46.08; 60.91; 72.15; 174.14; 175.07.

Bis((S)-2-carboxypyrrolidinium)-(2*S*,3*S*)-2,3-dihydroxysuccinate; T(*S,S*)-2Pro(*S*)

[(*S*)-Pro]$_2$-[(*S,S*)-Trtr]



$C_{14}H_{24}N_2O_{10}$

M = 380.35 g.mol^{-1}

White solid

Yield: 100%.

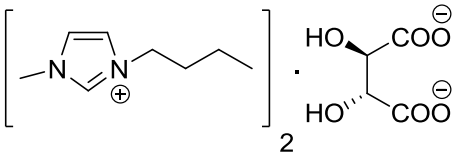
^{1}H NMR (300.18 MHz, D_2O), ppm: 2.00 (m, 3H); 2.35 (m, 1H); 3.35 (m, 2H); 4.17 (m, 1H); 4.66 (s, 2H).

6.6 Alkylimidazolium tartrates

6.6.1 General procedure for cross-metathesis

To corresponding ionic liquid [bmim]NTf_2 or [omim]NTf_2 (15 eq) was added bis-(tetrabutylphosphonium)-(*L*)-tartrate (1 eq) and water (33 eq). Resulting mixture was stirred overnight, decanted, water was evaporated and resulting compound was dried under vacuum line.

Bis(1-methyl-3-butyl-1H-imidazol-3-ium)-(2*R*,3*R*)-2,3-dihydroxysuccinate; [bmim]$_2$-[(*R,R*)-Trtr]



$C_{20}H_{34}N_4O_6$

M = 426.50 g.mol^{-1}

Light yellow oil

Yield: 100%.

DSC = -58°C (glass transition with relaxation).

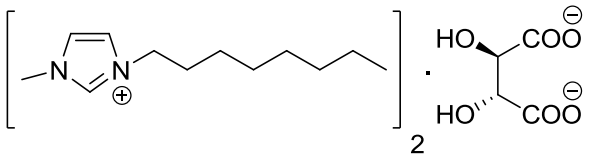
[α] $_D^{20}$ = +8.2 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.72 (t, 6H, J=7.4 Hz); 1.13 (m, 4H); 1.67 (m, 4H); 3.71 (s, 6H); 4.03 (t, 2H, J=7.1 Hz); 4.14 (s, 2H); 7.24 (m, 2H); 7.30 (m, 2H); 8.53 (s, 2H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.58; 18.71; 31.22; 35.54; 49.22; 73.84; 122.13; 123.38; 178.38.

Mass, IS- (H_2O/MeOH): 280, 212, 149. **IS+** (H_2O/MeOH): 139.

Bis(1-methyl-3-octyl-1H-imidazol-3-ium)-(2*R*,3*R*)-2,3-dihydroxysuccinate; [omim]$_2$-[(*R,R*)-Trtr]



$C_{28}H_{50}N_4O_6$

M = 538.72 g.mol^{-1}

Light yellow oil

Yield: 100%.

DSC = -43°C (glass transition with relaxation).

[α] $_D^{20}$ = +7.5 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.85 (t, 6H, J=6.9 Hz); 1.27 (m, 20H); 1.86 (m, 4H); 3.88 (s, 6H); 4.18 (t, 2H, J=7.0 Hz); 4.31 (s, 2H); 7.41 (t, 1H, J=1.7 Hz); 7.46 (t, 1H, J=1.7 Hz); 8.69 (s, 1H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 13.36; 21.95; 25.24; 27.96; 28.15; 29.12; 30.95; 35.55; 49.52; 73.84; 122.13; 123.41; 178.41.

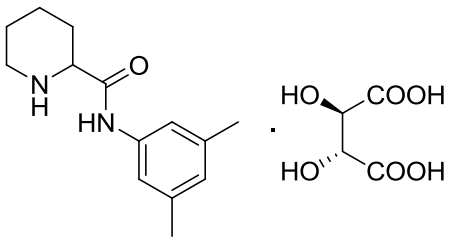
Mass, IS+ (H_2O/MeOH)**:** 195.

6.7 Other tartrates

(N-(3,5-dimethylphenyl)piperidine-2-carboxamide)-(2*R*,3*R*)-2,3-dihydroxysuccinate;

[Pipeco]-[(*R,R*)-Trtr]

Pipecoloxylidide (1 eq.) was added to the water solution of tartaric acid ((*R,R*)*;* 1 eq.). Resulting solution was stirred for 1 hour, evaporated and dried under vacuum line.



$C_{18}H_{26}N_2O_7$

M = 382.41 g.mol^{-1}

White solid

Yield: 100%.

Mp = 110°C.

[α] $_D^{20}$ = +7.9 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.64 (m, 2H); 1.85 (m, 3H); 2.10 (s, 6H); 2.40 (m, 1H); 3.04 (m, 1H); 3.44 (d, 1H); 4.14 (m, 1H); 4.44 (s, 2H); 7.13 (m, 3H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 17.08; 21.29; 21.48; 27.41; 43.87; 57.64; 72.85; 128.21; 128.42; 132.08; 135.99; 169.02; 176.27.

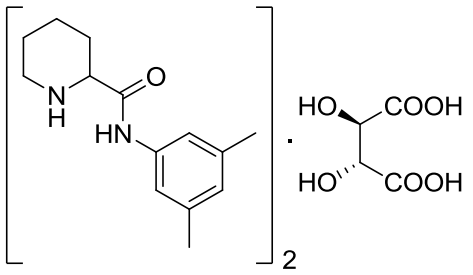
Mass, CI+ (NH_3): 233. **CI- (NH_3):** 280.

Elemental Analysis, Calculated for $C_{18}H_{26}N_2O_7$: C, 56.53; H, 6.85; N, 7.33. Found: C, 52.44; H, 6.52; N, 6.64.

Bis(N-(3,5-dimethylphenyl)piperidine-2-carboxamide)- (2*R*,3*R*)-2,3-dihydroxysuccinate;

[Pipeco]$_2$-[(*R,R*)-Trtr]

Pipecoloxylidide (2 eq.) was added to the water solution of tartaric acid ((*R,R*)*;* 1 eq.). Resulting solution was stirred for 1 hour, evaporated and dried under vacuum line.



$C_{32}H_{46}N_4O_8$

M = 614.73 g.mol^{-1}

White solid

Yield: 100%.

Mp = 95°C.

[α] $_D^{20}$ = +8.2 (c 1, H_2O).

^{1}H NMR (300.18 MHz, D_2O), ppm: 1.63 (m, 4H); 1.68 (m, 6H); 2.09 (s, 12H); 2.34 (m, 2H); 3.03 (m, 2H); 3.41 (m, 2H); 4.10 (m, 2H); 4.22 (s, 2H); 7.12 (m, 6H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 17.08; 21.32; 21.49; 27.43; 43.87; 48.86; 57.64; 128.2; 128.4; 132.08; 135.98; 169.06.

Mass, CI+ (NH_3): 233. **CI+ (NH_3):** 149.

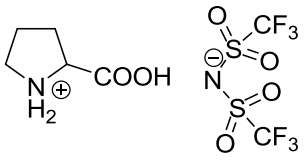
Elemental Analysis, Calculated for $C_{32}H_{46}N_4O_8$: C, 62.52; H, 7.54; N, 9.11. Found: C, 58.41; H, 7.68; N, 8.65.

6.8 Bis(trifluoromethylsulfonyl)imides

6.8.1 General procedure for bis(trifluoromethylsulfonyl)imides preparation

Corresponding amine or amino acid (1 eq.) was dissolved in acetonitrile and bis(trifluoromethylsulfonyl)imide (1 eq.) was added. Resulting solution was stirred for 30 minutes, evaporated and dried under vacuum line.

Prolinium bis(trifluoromethylsulfonyl)imide; [HPro]NTf$_2$



$C_7H_{10}F_6N_2O_6S_2$

M = 396.28 g.mol^{-1}

White wax

Yield: 100%.

Mp = 72°C.

^{1}H NMR (300.18 MHz, MeOD), ppm: 2.03 (m, 3H); 2.38 (m, 1H); 3.27 (m, 2H); 4.32 (t, 1H, J=7.6 Hz).

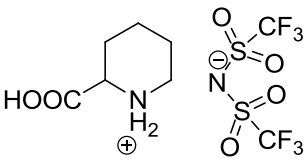
^{13}C NMR (75.48 MHz, MeOD), ppm: 23.22; 28.08; 45.82; 59.41; 113.50-126.24 (q, 2C, J=320 Hz); 170.00.

^{19}F NMR (282.37 MHz, MeOD), ppm: -80.61.

Mass, IS+ (MeOH)**:** 116. **ES-**(MeOH)**:** 280.

Elemental Analysis, Calculated for $C_7H_{10}F_6N_2O_6S_2$: C, 21.22; H, 2.54; N, 7.07. Found: C, 20.10; H, 2.14; N, 6.77.

2-carboxypiperidinium bis(trifluoromethylsulfonyl)imide; [HPip]NTf$_2$



$C_8H_{12}F_6N_2O_6S_2$

M = 410.31 g.mol^{-1}

White wax

Yield: 100%.

Mp = -15°C.

^{1}H NMR (300.18 MHz, MeOD), ppm: 1.66 (m, 3H); 1.89 (m, 2H); 2.28 (m, 1H); 3.01 (m, 1H); 3.36 (m, 1H); 3.93 (m, 1H).

^{13}C NMR (75.48 MHz, MeOD), ppm: 21.50; 25.90; 43.64; 56.49; 113.46-126.19 (q, 2C, J=320 Hz); 169.84.

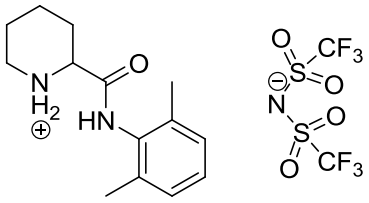
^{19}F NMR (282.37 MHz, MeOD), ppm: -79.27.

Mass, CI+ (NH_3): 206; 130. **CI- (NH_3):** 280.

Elemental Analysis, Calculated for $C_8H_{12}F_6N_2O_6S_2$: C, 23.42; H, 2.95; N, 6.83. Found: C, 23.19; H, 2.64; N, 6.33.

N-(2,6-dimethylphenyl)piperidinium-2-carboxamide bis(trifluoromethylsulfonyl)imide;

[HPipeco]NTf_2



$C_{16}H_{21}F_6N_3O_5S_2$

M = 513.48 g.mol^{-1}

White solid

Yield: 100%.

Mp = 204°C.

^{1}H NMR (300.18 MHz, MeOD), ppm: 3.02 (m, 3H); 3.55 (s, 6H); 3.61 (m, 1H); 4.39 (m, 1H); 4.80 (m, 1H); 5.38 (m, 1H); 8.33 (large s, 1H); 8.51 (m, 3H); 9.51 (s, 1H).

^{13}C NMR (75.48 MHz, MeOD), ppm: 16.94; 21.48; 21.84; 27.68; 43.62; 57.82; 113.68-126.13 (q, 2C, J=319 Hz); 127.49; 127.90; 132.87; 135.34; 167.49.

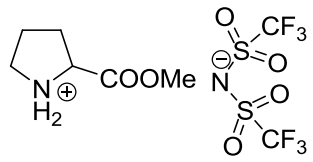
^{19}F NMR (282.37 MHz, MeOD), ppm: -79.51.

Mass, CI+ (NH_3): 233. **CI- (NH_3):** 280.

Elemental Analysis, Calculated for $C_{16}H_{21}F_6N_3O_5S_2$: C, 37.43; H, 4.12; N, 8.18. Found: C, 37.33; H, 3.80; N, 8.08.

2-(methoxycarbonyl)pyrrolidinium bis(trifluoromethylsulfonyl)imide; [HProOMe]NTf_2

Proline (1 eq.) was dissolved in methanol and bis(trifluoromethylsulfonyl)imide (1 eq.) was added. Resulting solution was stirred for 1 hour, evaporated and dried under vacuum line.



$C_8H_{12}F_6N_2O_6S_2$

M = 410.31 g.mol^{-1}

Colorless oil

Yield: 100%.

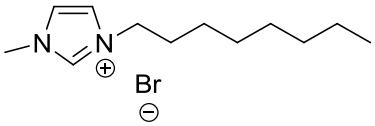
^{1}H NMR (300.18 MHz, CD_3CN), ppm: 1.92-2.10 (m, 3H); 2.31 (m, 1H); 3.35 (m, 2H); 3.79 (s, 3H); 4.33 (m, 1H).

^{13}C NMR (75.48 MHz, CD_3CN), ppm: 23.26; 27.95; 46.86; 53.14; 59.58; 113.27-126.01 (q, 2C, J=320 Hz); 169.02.

6.9 Commonly used ionic liquids

1-methyl-3-octyl-1H-imidazol-3-ium bromide; [omim]Br

1-methylimidazolium (1 eq.) was mixed with 1-*n*-bromooctane (1 eq.) without solvent. Resulting mixture was heated at 50 °C overnight. Resulting compound was dried under vacuum line.



$C_{12}H_{23}BrN_2$

M = 275.23 g.mol^{-1}

Yellow viscous oil

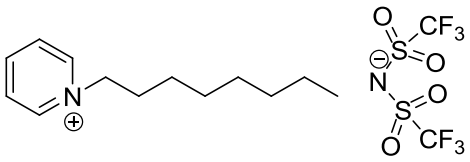
Yield: 98%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 0.87 (s, 3H); 1.25 (m, 10H); 1.92 (m, 2H); 4.13 (s, 3H); 4.32 (t, 2H, J=7.3 Hz); 7.38 (t, 1H, J=1.8 Hz); 7.52 (t, 1H, J=1.8 Hz); 10.44 (s, 1H).

^{13}C NMR (75.48 MHz, $CDCl_3$), ppm: 14.07; 22.58; 26.26; 28.94; 29.02; 30.32; 31.67; 36.8; 50.22; 76.66; 77.08; 77.51; 103.28; 121.77; 123.49.

N-octylpyridinium bis(trifluoromethylsulfonyl)imide; [oPy]NTf_2

Octylpyridinium bromide (1 eq.) was added to the water solution of lithium bis(trifluoromethylsulfonyl)imide (1 eq.). Resulting mixture was stirred for 1 hour. Precipitated oil was decanted, washed with distilled water and dried under vacuum line.



$C_{15}H_{22}F_6N_2O_4S_2$

M = 472.47 g.mol^{-1}

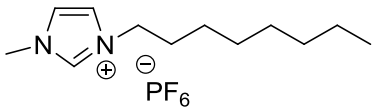
Yellow oil

Yield: 87%.

^{1}H NMR (300.18 MHz, CD_3CN), ppm: 0.70 (t, 3H, J=7.1 Hz); 1.15 (m, 10H); 1.75 (m, 2H); 4.29 (t, 2H, J=7.6 Hz); 7.81 (pseudo-t, 2H, J=6.8 Hz); 8.29 (t, 1H, J=7.8 Hz); 8.48 (d, 2H, J=5.7).

1-methyl-3-octyl-1H-imidazol-3-ium hexafluorophosphate; [omim]PF_6

1-methyl-3-octylimidazolium bromide (1 eq.) was added to the water solution of hexafluorophosphoric acid (1 eq.). One equivalent of 1M KOH solution was added to neutralize the mixture. Resulting mixture was stirred for 1 hour. Precipitated oil was decanted, washed with distilled water and dried under vacuum line.



$C_{12}H_{23}F_6N_2P$

M = 340.29 g.mol^{-1}

Yellow oil

Yield: 86%.

^{1}H NMR (300.18 MHz, CD_3Cl), ppm: 0.90 (t, 3H, J= 7 Hz); 1.28-1.34 (m, 10H); 1.89 (m, 2H); 3.96 (s, 3H); 4.18 (t, 2H, J= 7.5 Hz); 7.35 (s, 1H); 8.75 (s, 1H).

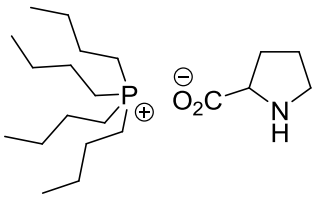
6.10 Tetrabutylphosphoniums

Before the synthesis commercial [PBu_4]OH needs to be purified from [PBu_4]Cl. To do this, it was extracted by CH_2Cl_2, dried under reduced pressure (only in order to eliminate residue of

organic solvent), diluted with distilled water and titrated with HCl to determine exact concentration.

Tetrabutylphosphonium pyrrolidine-2-carboxylate; [PBu_4]-[(Rac)-Pro]

To the proline was added appropriate volume of solution [PBu_4]OH. Resulting mixture was stirred for 15 minutes; evaporated to dryness under reduced pressure and dried under the vacuum line.



$C_{21}H_{44}NO_2P$

M = 359.52 $g.mol^{-1}$

Colorless oil

Yield: 100%.

^{1}H NMR (300.18 MHz, D_2O), ppm: 0.75 (t, 3H, J=7.2); 1.17-1.43 (m, 17H); 1.60 (m, 3H); 1.98 (m, 9H); 2.70 (m, 1H); 2.96 (m, 1H); 3.43 (m, 1H).

^{13}C NMR (75.48 MHz, D_2O), ppm: 12.53; 17.32; 17.96; 22.67 (d, 4C, J=4.5 Hz); 23.19 (d, 4C, J=15.3 Hz); 24.80; 30.33; 45.96; 61.43; 180.66.

^{31}P NMR (121.49 MHz, $CDCl_3$), ppm: 33.66 (s).

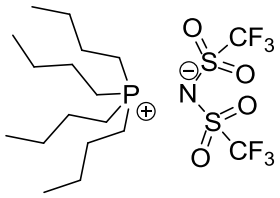
Mass, IS+ (H_2O/MeOH)**:** 259.

Tetrabutylphosphonium bis(trifluoromethylsulfonyl)imide; [PBu_4]NTf_2

Method A. To the lithium bis(trifluoromethylsulfonyl)imide was added appropriate volume of solution [PBu_4]OH. Then, 1 equivalent of 1M HCl solution was added to neutralize the reaction media. Resulting mixture was stirred for 1 hour; precipitated compound was filtered, washed with water and dried under the vacuum line.

Method B. To the ionic liquid [bmim]NTf_2 or [omim]NTf_2 (1 eq) was added bis-(tetrabutylphosphonium)-(*L*)-tartrate (1 eq) and water (30 eq). Resulting mixture was stirred

overnight; precipitated compound was filtered, washed with water and dried under the vacuum line.



$C_{18}H_{36}F_6NO_4PS_2$

M = 539.58 g.mol^{-1}

White wax

Yield: 100% (Method A).

Mp = 71°C.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 0.99 (m, 24H); 1.53 (m, 32H); 3.12 (m, 16H).

^{13}C NMR (75.48 MHz, $CDCl_3$), ppm: 13.28; 18.21-18.84 (d, 4C, J=47.6 Hz); 23.47-23.53 (d, 4C, J=4.7 Hz); 23.70-23.91 (d, 4C, J=15.4 Hz); 113.67-126.30 (q, 2C, J=327 Hz).

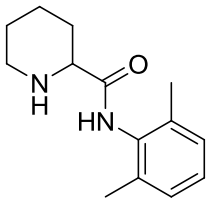
^{19}F NMR (282.37 MHz, $CDCl_3$), ppm: -78.79.

^{31}P NMR (121.49 MHz, $CDCl_3$), ppm: 33.23 (m).

6.11 Pipecoloxylidide

Pipecoloxylidide (N-(2,6-dimethylphenyl)piperidine-2-carboxamide); Pipeco

To the water solution of pipecoloxylidide chlorohydrate was added 1M KOH solution to obtain pH ≥12. Resulting mixture was extracted 3 times with CH_2Cl_2. Combined organic layers were evaporated under reduced pressure, resulting in final product.



$C_{14}H_{20}N_2O$

M = 232.32 g.mol^{-1}

White solid

Yield: 100%.

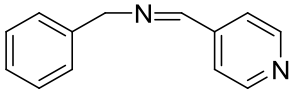
Mp =119°C.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 1.36-1.72 (m, 3H); 1.92 (m, 3H); 2.10 (m, 1H); 2.22 (s, 6H); 2.79 (m, 1H); 3.11 (m, 1H); 3.45 (m, 1H); 7.07 (m, 3H); 8.28 (large s, 1H).

6.12 Compounds, used to perform model reactions

1-phenyl-N-(pyridin-4-ylmethylene)methanamine

To 30 mL of CH_2Cl_2 and Na_2SO_4 was added 0.56 mL of pyridine-4-carboxaldehyde (1 eq., ρ=1.14) and 0.47 mL of benzylamine (1 eq., ρ=0.98). The solution was stirred for 2 hours, filtered and evaporated.



$C_{13}H_{12}N_2$

M = 196.25 g.mol^{-1}

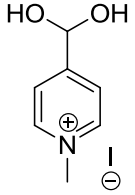
Yellow solid

Yield: 100%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 4.73 (s, 2H); 7.15 (m, 1H); 7.31 (m, 3H); 7.33 (m, 3H); 7.69 (m, 2H); 8.30 (s, 1H).

Pyridin-4-ylmethanediol

To 25 mL of CH_3CN was added 0.47 mL of pyridine-4-carboxaldehyde (1 eq., ρ=1.14) and 0.62 mL of methyliodide (2 eq., ρ=2.28). The solution was stirred for 12 hours at 40°C. Then, it was filtered, evaporated and dried under vacuum line.



$C_7H_{10}INO_2$

M = 267.06 g.mol^{-1}

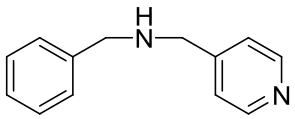
White solid

Yield: 95%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 4.39 (s, 3H); 6.12 (s, 1H); 8.11 (d, 2H, J=6.5); 8.80 (d, 2H, J=6.5).

N-benzyl-1-(pyridin-4-yl)methanamine

To 30 mL of CH_2Cl_2 and Na_2SO_4 was added 0.56 mL of pyridine-4-carboxaldehyde (1 eq., ρ=1.14) and 0.47 mL of benzylamine (1 eq., ρ=0.98). The solution was stirred for 2 hours, filtered and evaporated. Obtained compound was dissolved in 20 mL of methanol and 4 equivalents of $NaBH_4$ were added slowly. The reaction mixture was stirred for 6 hours. Then, 10 mL of water was added and reaction mixture was evaporated. Then, 25 mL of 1M KOH was added to obtain pH≥12 and water layer was extracted 3 times with CH_2Cl_2. Combined organic layers were dried under Na_2SO_4, filtered and evaporated.



$C_{13}H_{14}N_2$

M = 198.26 g.mol^{-1}

Yellow solid

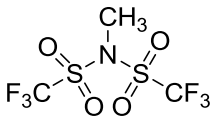
Yield: 74%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 1.77 (s, 1H); 3.72 (s, 2H); 3.73 (s, 2H); 7.19-7.26 (m, 7H); 8.46 (d, 2H).

^{13}C NMR (75.48 MHz, $CDCl_3$), ppm: 51.81; 63.06; 121.15; 123.07; 127.23; 128.15; 128.54; 139.76; 149.52; 149.73.

1,1,1-trifluoro-N-methyl-N-(trifluoromethylsulfonyl)methanesulfonamide; $MeNTf_2$

Into 50 mL flask were charged bis(trifluoromethylsulfonyl)imide (1 eq) and 10x excess of trimethylortoacetate (10 eq., ρ=0.94). The resulting solution was refluxed under N_2 for 12 hours. The excess of trimethylortoacetate was removed via vacuum.



$C_3H_3F_6NO_4S_2$

M = 295.18 g.mol^{-1}

Transparent liquid

Yield: 81%.

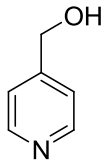
^{1}H NMR (300.18 MHz, CD_3CN), ppm: 3.14 (s, 3H).

^{13}C NMR (75.48 MHz, CD_3CN), ppm: 28.99 (m, 1C); 109.28-120.54 (q, 2C).

^{19}F NMR (282.37 MHz, CD_3CN), ppm: -79.88.

Pyridin-4-ylmethanol

To the solution of pyridine-4-carboxaldehyde (1 eq., ρ=1.14) in 15 mL of CH_3CN were added slowly 2 equivalents of $NaBH_4$. The reaction mixture was stirred for 12 hours. Then, 10 mL of water was added and reaction mixture was evaporated. Another 25 mL of water was added and water layer was extracted 3 times with CH_2Cl_2. Combined organic layers were dried under Na_2SO_4, filtered and evaporated.



C_6H_7NO

M = 109.13 g.mol^{-1}

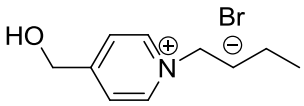
White solid

Yield: 37%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 4.70 (s, 2H); 7.44 (d, 2H, J=6.1); 8.49 (d, 2H, J=6.1).

1-butyl-4-(hydroxymethyl)pyridinium bromide

To the solution of pyridin-4-ylmethanol (1 eq) in 30 mL of MeOH was added slowly 1 equivalent of bromobutane. The reaction mixture was stirred for 12 hours at 50°C. The solvent was evaporated and the resulting compound was washed with ether two times, filtered and dried in vacuum.



$C_{10}H_{16}BrNO$

M = 246.14 g.mol^{-1}

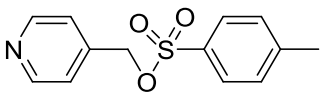
Red solid

Yield: 21%.

^{1}H NMR (300.18 MHz, MeOD), ppm: 1.04 (m, 3H); 1.43 (m, 2H); 2.02 (m, 2H); 4.63 (m, 2H); 4.72 (s, 2H); 7.48 (d, 2H, J=5.4); 8.52 (d, 2H, J=5.4).

Pyridin-4-ylmethyl 4-methylbenzenesulfonate

To the solution of pyridin-4-ylmethanol (1 eq) in 10 mL of CH_3CN was added 1 equivalent of tosylchloride. Then, 1 equivalent of triethylamine was added. The reaction mixture was stirred for 2 days. The solvent was evaporated and the resulting compound was dissolved in CH2Cl2 and extracted two times with water. Combined water layers was evaporated and dried in vacuum.



$C_{13}H_{13}NO_3S$

M = 263.31 g.mol^{-1}

White solid

Yield: 62%.

^{1}H NMR (300.18 MHz, $CDCl_3$), ppm: 1.30 (s, 3H); 3.08 (s, 2H); 7.15 (m, 4H); 7.37 (d, 2H, J=8.4) 7.71 (d, 2H, J=8.4).

6.13 ELLEs

6.13.1 General procedure of ELLE

The biphasic chiral extraction system was established in 5 ml test tube by adding ½ equivalent of chiral ionic liquid to 10 equivalents of commercial hydrophobic ionic liquid (about 1 mL). Ionic liquid phase was enriched by 1 equivalent of racemic compound to be resolved and the system was stirred for 12 hours at RT to let molecules of host and racemate interact. After that, 100 equivalents of water were added and the biphasic system was stirred for additional 3

hours with the goal to extract one of enantiomers. When no clear phase boundary was visible, the mixture was centrifuged. Water layer was separated, evaporated and dried under vacuum line.

6.13.2 General procedure of cross-metathesis

The biphasic chiral extraction system was established in 5 ml test tube by adding ¼ equivalent of chiral tartaric acid-based ionic liquid to 10 equivalents of commercial hydrophobic ionic liquid (about 1 mL). Ionic liquid phase was enriched by 1 equivalent of racemic compound to be resolved and the system was stirred for 2 hours at RT to let molecules of host and racemate interact. After that, 20 equivalents of water were added and the biphasic system was stirred for additional 12 hours with the goal to extract one of enantiomers. When no clear phase boundary was visible, the mixture was centrifuged. Water layer was separated, evaporated and dried under vacuum line.

6.13.3 Experimental procedure of the best example of cross-metathesis

The biphasic chiral extraction system was established in 5 ml test tube by adding ¼ equivalent of **[PBu_4]$_2$-[(*R,R*)-Trtr]**, (66,7 mg), to 10 equivalents of **[omim]NTf_2** (951 mg). Ionic liquid phase was enriched by 1 equivalent of **[HPipeco]NTf_2** (208 mg) and the system was stirred for 2 hours at 50°C to let molecules of host and racemate interact. After cooling the mixture, 20 equivalents of distilled water were added, and the biphasic system was stirred for additional 12 hours. Water layer was separated, evaporated and dried under vacuum line to give 13 mg of **[HPipeco]$_2$-[Trtr]**.

To perform chiral HPLC analysis, 1 mg of dry (the presence of water affect the chromatogram) extracted compound was dissolved in the mixture of 0.5 mL *i*-PrOH/ 0.5 mL heptane/ 10 µL diethylamine. HPLC conditions are described in the part 6.1. Enantiomeric excess of 30% was determined.

7 References

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List of abbreviations

3D: three dimensional

A: substrate

AA: Amino acid

absol: absolute

Ac: Acetyl

Ala: alanine

Alk: Alkyl

Ar: Aromatic

bmim: 1-butyl-3-methyl imidazolium

Bn: Benzyl

Boc: tert-butyloxycarbonyl

Bu: Butyl

c: concentration

C: host

CAS: Chemical Abstract Substance

Cbz: Carboxybenzyl

CCS: centrifugal contactor separators

CD: cyclodextrin

CI: chemical ionization

CIL: Chiral ionic liquid

CILBs: chiral ionic liquids benzathines

CSP: chiral stationary phase

d: doublet

DACH: 1,2-diaminocyclohexane

DIEA: N,N-Diisopropylethylamine

DMF: N,N-Dimethylformamide

DMSO: Dimethylsulfoxyde

DNB: dinitrobenzene

Dodec: Dodecyl

DSC: Differential Scanning Calorimetry

e: ethyl

ECOENG 212: 1-ethyl-3-methylimidazolium ethylsulfate

ee: enantiomeric excess

EI: Electronic impact

ELLE: Enantioselective liquid-liquid extraction

ELS: Electrophoretic light scattering

emim: 1-ethyl-3-methyl imidazolium

eq.: equivalent

ESI: Electrospray ionization

Et: Ethyl

Et_2O: Diethylether

EtOAc: Ethyl acetate

F: feed

FAB: Fast Atoms Bombarding

FTIR - Fourier Transform Infrared Spectroscopy

GS: Gas chromatography

h: hour

HE: Hydroxyethyl

His: histidine

hmim: 1-hexyl-3-methyl imidazolium

HP: Hydroxypropyl

HPLC: High Performance Liquid Chromatography

HRMS: High Resolution Mass Spectroscopy

Hz: Hertz

IL: Ionic liquid

im: imidazole

INTENANT: INTegrated synthesis & purification of single ENANTiomers

i-Pr: iso-Propyl

IR: Infra-red

J: coupling constant

L: ligand

LI: Liquide ionique

LIC: Liquide ionique chiral

m: methyl

M: molar

Me: methyl

MHz: Megahertz

min: Minute

Mp: Melting point

MS: Mass spectrometry

M_w: Molecular weight

N: ammonium

nd: not determined

NIR: Near-infrared

N_{min}: minimal number of required fractional extraction steps

NMR: Nuclear magnetic resonance

NTf_2: bis(trifluoromethane) sulfonate

o: octyl

omim: 1-octyl-3-methyl imidazolium

P: phosphonium

PBu_4: Tetrabutylphosphonium

Ph: Phenyl

Pip: pipecolinic acid

Pipeco: pipecoloxylidide

ppm: part per millions

Pr: Propyl

Pro: proline

py: pyridinium

q: quadruplet

quant.: quantitatively

R: raffinate (in extractions)

R: substituent (defined in each particular case)

rpm: Revolutions per minute

rt: room temperature

RT: Room Temperature

RTIL: Room-Temperature Ionic Liquid

s: singlet

S: solvent

Sip: silaproline

t: triplet

TBA: Tetrabutylammonium

TBP: Tetrabutylphosphonium

t-Bu: tert-butyl

Tf: Trifluorosulfonyl

$T_{GT:}$ Glass transition temperature

THF: tetrahydrofuran

TLC: Thin Layer Chromatography

T_m: melting point

Trp: tryptophan

Trtr: Tartrate

Ts: Tosyl

TSIL: Task-Specific Ionic Liquids

UV: Ultra-violet

w/s: without solvent

W: wash

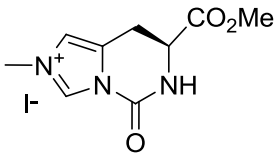
WP: Work Package

α_D: optical rotation

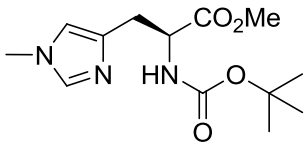
α_{op}: operational selectivity

δ: Chemical shift

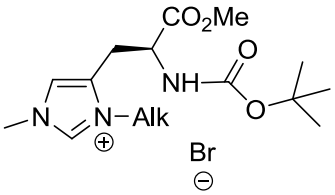
8 List of compounds formulas and their codes



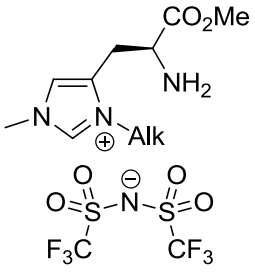
H1



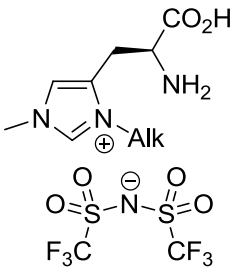
H2



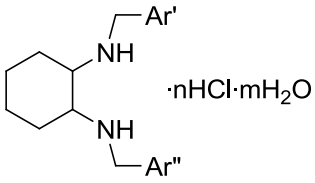
H3a: Alk= *n*-Bu
H3b: Alk= *n*-Oct
H3c: Alk= *n*-Dodec



H5a: Alk= *n*-Bu
H5b: Alk= *n*-Oct

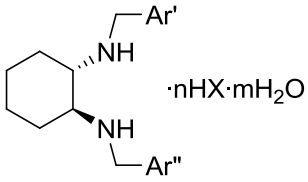


H6a: Alk= *n*-Bu
H6b: Alk= *n*-Oct
H6c: Alk= *n*-Dodec



Racemic

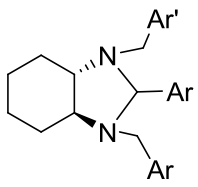
D4,4Rac: Ar'= 4-pyridyl; Ar"= 4-pyridyl
D3,3Rac: Ar'= 3-pyridyl; Ar"= 3-pyridyl



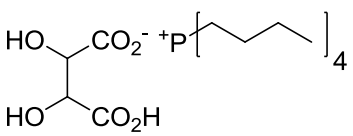
(*S,S*)

D4,4: Ar'= 4-pyridyl; Ar"= 4-pyridyl
D3,3: Ar'= 3-pyridyl; Ar"= 3-pyridyl
D2,2: Ar'= 2-pyridyl; Ar"= 2-pyridyl
D4,Ph: Ar'= 4-pyridyl; Ar"= phenyl
D3,Ph: Ar'= 3-pyridyl; Ar"= phenyl
D2,Ph: Ar'= 2-pyridyl; Ar"= phenyl
D4,3: Ar'= 4-pyridyl; Ar"= 3-pyridyl
D4,2: Ar'= 4-pyridyl; Ar"= 2-pyridyl
D3,2: Ar'= 3-pyridyl; Ar"= 2-pyridyl

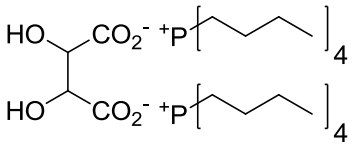
X= Cl; BF_4; PF_6; NTf_2



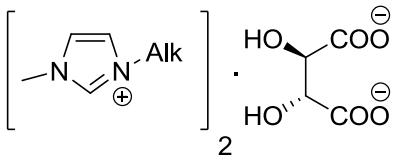
D2,2,2: Ar'=Ar= 2-pyridyl
D4,Ph,Ph: Ar'= 4-pyridyl; Ar= phenyl



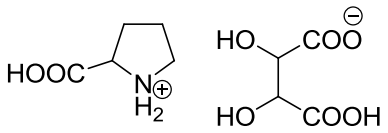
T(R,R)-P$_4$: (*R,R*)-tartrate
T(S,S)-P$_4$: (*S,S*)-tartrate
T(R,S)-P$_4$: (*R,S*)-tartrate
T(Rac)-P$_4$: (Rac)-tartrate



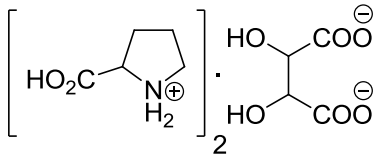
T(R,R)-2P$_4$: (*R,R*)-tartrate
T(S,S)-2P$_4$: (*S,S*)-tartrate
T(R,S)-2P$_4$: (*R,S*)-tartrate
T(Rac)-2P$_4$: (Rac)-tartrate



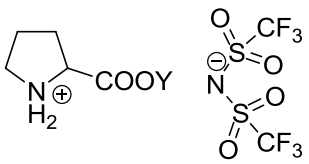
[bmim]2-[(*R,R*)-Trtr]: Alk= *n*-Bu
[omim]2-[(*R,R*)-Trtr]: Alk= *n*-Oct



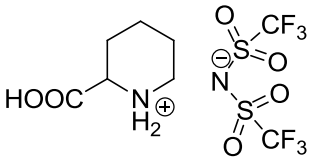
T(R,R)-Pro(S): (*R,R*)-tartrate; (S)-Pro
T(R,R)-Pro(Rac): (*R,R*)-tartrate; (Rac)-Pro
T(S,S)-Pro(S): (*S,S*)-tartrate; (S)-Pro



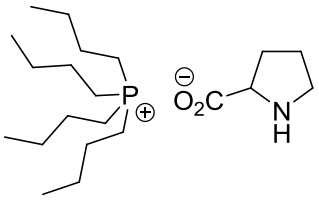
T(R,R)-2Pro(S): (*R,R*)-tartrate; (S)-Pro
T(R,R)-2Pro(Rac): (*R,R*)-tartrate; (Rac)-Pro
T(S,S)-2Pro(S): (*S,S*)-tartrate; (S)-Pro



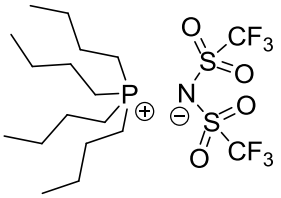
[HPro]NTf$_2$: Y= H
[HProOMe]NTf$_2$: Y= Me



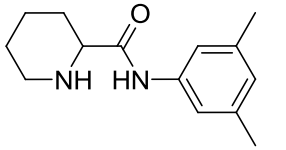
[HPip]NTf$_2$



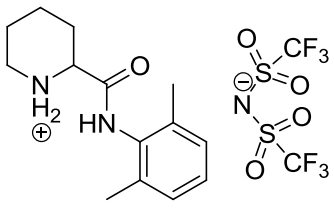
[PBu$_4$]-[(Rac)-Pro]



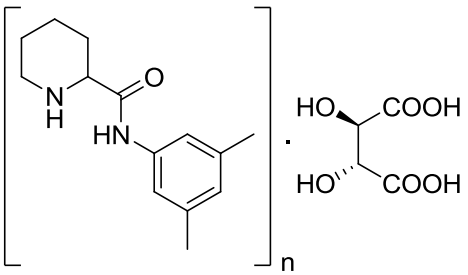
[PBu$_4$]NTf$_2$



Pipeco: pipecoloxylidide



[HPipeco]NTf$_2$



[Pipeco]-[(*R,R*)-Trtr]: n= 1
[Pipeco]$_2$-[(*R,R*)-Trtr]: n= 2

9 Articles and conferences

9.1 List of publications

JOURNAL PUBLICATIONS

1. Viacheslav Zgonnik, Silvia Gonella, Marie-Rose Mazières, Frédéric Guillen, Gérard Coquerel, Nathalie Saffon, Jean-Christophe Plaquevent. Design and scalable synthesis of new chiral selectors. Part 2: Chiral ionic liquids derived from diaminocyclohexane and histidine. *Organic Process Research & Development*, **2011**, doi:10.1021/op200082a
2. Viacheslav Zgonnik, Marie-Rose Mazières & Jean-Christophe Plaquevent. 1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate. *Encyclopedia of Reagents for Organic Synthesis (e-EROS)*, **2010**. doi=10.1002/047084289X.rn01221

BOOK CHAPTERS

1. Chapter 7: Chiral ionic liquids for asymmetric reactions. Annie-Claude Gaumont, Yves Génisson, Frédéric Guillen, Viacheslav Zgonnik, Jean-Christophe Plaquevent. In the book: *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications.* John Wiley & Sons, Inc., **2011**, ISBN: 978-0-470-64136-1 doi:10.1002/9781118087992.ch7

SCIENCE POPULARIZATION

1. V. Zgonnik, J.-C. Plaquevent, M.-R. Mazières, Y. Génisson, M. Baltas. Les liquides ioniques: de nouveaux solvants pour une chimie plus verte. *Petit chimiste illustré*, p.28. (Brochure de journal quotidien «La Dépêche» éditée par CNRS pour l'Année internationale de chimie 2011).

9.2 Participation in congresses and conferences

1. 6th International Chemistry Conference Toulouse-Kiev. 30-31 May 2011, Toulouse, France. (*Poster in English*)

   V. Zgonnik, F. Guillen, M.-R. Mazières, G. Coquerel, J.-C. Plaquevent. ELLE & IL: **Enantioselective liquid-liquid extraction and ionic liquids**. Book of abstracts, p. P100
2. INTENANT Final Technical Meeting. 12-13 May 2011, Berlin, Germany. *(Poster in English)*

   V. Zgonnik, F. Guillen, M.-R. Mazières, G. Coquerel, J.-C. Plaquevent. ELLE & IL: **Enantioselective liquid-liquid extraction and ionic liquids**. (available online *http://www.intenant.eu* only for INTENANT participants)
3. 5th INTENANT Technical Meeting & Workshop. 22-24 November 2010. Bayer Technology Services, Leverkusen, Germany. *(Oral presentation and poster. Both in English)*

Viacheslav Zgonnik **Enantioselective Liquid-Liquid Extraction using chiral ionic liquids.** (available online http://www.intenant.eu only for INTENANT participants)

4. First LSPCMIB-Brazil meeting. 8 November 2010, Paul Sabatier University, Toulouse, France. *(Oral presentation in English)*

   Viacheslav Zgonnik **Chiral ionic liquids as new tools towards liquid-liquid resolutions**. (No abstracts were published, only titles)

5. 4th INTENANT Technical Meeting & Workshop. 16-18 June 2010. IRCOF Institute, Rouen, France. *(Oral presentation and poster. Both in English)*

   Viacheslav Zgonnik **Chiral Ionic Liquids for Enantioselective Extractive Resolution**, (available online http://www.intenant.eu only for INTENANT participants)

6. INTENANT 3rd Technical Meeting & Workshop on Biological Synthesis, Stockholm University & Astra Zeneca AB, 25-27 November 2009, Stockholm and Södertälje, Sweden. *(Oral presentation and poster. Both in English)*

   Viacheslav Zgonnik **Chiral Ionic Liquids for Enantioselective Extractive Resolution**, (available online http://www.intenant.eu only for INTENANT participants)

7. Project Meeting of INTENANT 3-4 September 2009 at DECHEMA, Frankfurt/Main, Germany. *(only participation)*

8. INTENANT 2nd Technical Meeting. 11-12 June 2009, Zurich, Switzerland. *(Oral presentation and poster. Both in English)*

   Viacheslav Zgonnik, Frédéric Guillen, Marie-Rose Mazières, Jean-Christophe Plaquevent. **Chiral Ionic Liquids for Enantioselective Extractive Resolution**, (available online http://www.intenant.eu only for INTENANT participants)

9. INTENANT 1st technical meeting, Magdeburg, Germany, 15 December 2008. *(Was not attended. Presentation was held by J.-C. Plaquevent)*

   C. Rougeot, V. Zgonnik, M.R. Maziéres, F. Guillen, G. Coquerel, J.C. Plaquevent. **Chiral macrocycles and chiral ionic liquids: towards new processes for resolution and chiral recognition**. (available online http://www.intenant.eu only for INTENANT participants)

Extraction Liquide-Liquide Enantiosélective et Liquides Ioniques

Viacheslav Zgonnik

Directeur de thèse : Dr. Jean-Christophe Plaquevent

Laboratoire de Synthese et Physico-Chimie de Molecules d'Interet Biologique (LSPCMIB, UMR5068)
Université Paul Sabatier, 118 Route de Narbonne, F-31062 Toulouse Cedex 9, France

Thèse soutenue à Toulouse le 19 juillet 2011
Discipline : Chimie Moléculaire

Résumé :

L'extraction liquide-liquide énantiosélective (ELLE) consiste en l'extraction d'un énantiomère à partir d'un mélange racémique par transfert entre deux phases liquides. Cette technologie est très prometteuse pour l'obtention des composés énantiopurs et devient l'objet d'une forte attention les dernières années grâce au développement de l'équipement approprié qui permet de réduire le temps et le prix de la séparation des énantiomères. L'objectif essentiel pour l'introduction d'ELLE dans le monde industriel est la découverte d'hôtes chiraux fiables, peu chers, durables, sélectifs et applicables à une large gamme de substances chirales. Dans ce travail, la possibilité d'effectuer l'ELLE dans un milieu ionique chiral a été vérifiée. De nombreux nouveaux liquides ioniques chiraux ont été préparés pour jouer le rôle des hôtes chiraux. Le meilleur exemple montre un excès énantiomérique de 30% et une sélectivité opérationnelle de 1,97. Ceci représente le premier exemple d'ELLE utilisant les liquides ioniques chiraux et sans usage d'ions métalliques.

Mots clés : Liquides ioniques ; Chiralité ; Énantiosélectivité ; Extractions Liquide-Liquide.

Extraction Liquide-Liquide Enantiosélective et Liquides Ioniques

Viacheslav Zgonnik

Directeur de thèse : Dr. Jean-Christophe Plaquevent

Laboratoire de Synthese et Physico-Chimie de Molecules d'Interet Biologique (LSPCMIB, UMR5068)
Université Paul Sabatier, 118 Route de Narbonne, F-31062 Toulouse Cedex 9, France
Thèse soutenue à Toulouse le 19 juillet 2011
Discipline : Chimie Moléculaire

Abstract :

Enantioselective liquid-liquid extraction (ELLE) is an implementation of the extraction of one enantiomer from a racemic mixture by the transfer between two liquid phases. This technology is very promising for obtaining enantiopure compounds and becomes the object of much attention in recent years after the development of appropriate equipment that reduces the time and cost of the separation of enantiomers. The major objective for the successful introduction of ELLE to industrial world is the discovery of reliable, inexpensive and durable chiral hosts selective for a wide range of chiral substances. In this work the possibility of performing ELLE in chiral ionic liquids environment was verified. Many new chiral ionic liquids were prepared to play the role of chiral hosts. The best example shows enantiomeric excess of 30% and operational selectivity of 1.97. This represents the first example of using chiral ionic liquids in ELLE and without metallic ions.